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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

MEMORANDUM

DATE: **March 27, 2018**

SUBJECT: **Flumethrin**. Draft Human Health Risk Assessment for Registration Review

PC Code: 036007
Decision No.: 517456
Petition No.: NA
Risk Assessment Type: Single Chemical
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40 CFR: NA

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The Pesticide Re-Evaluation Division (PRD) requested that the Health Effects Division (HED) conduct a draft risk assessment (DRA) for the pyrethroid insecticide, flumethrin. This document contains HED's DRA to support registration review. The most recent quantitative human health risk assessment was conducted in 2012 (D392125, C. Smith). The risk assessment and the occupational and residential exposure assessment were provided by Monica Hawkins and the hazard characterization, and endpoint selection were provided by Evisabel Craig. This assessment addresses exposure and risk associated with the use of flumethrin only.

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1.0 Executive Summary

Flumethrin is a Type II synthetic pyrethroid, which typically produce a distinct poisoning syndrome characterized by choreoathetosis (sinuous writhing of the whole body) and excessive salivation also known as CS syndrome. The only registered end-use product for flumethrin is a pet collar that contains both flumethrin and imidacloprid as the active ingredients. There are two different sizes of collars, both of which contain 4.5% flumethrin. The small collar weighs 12.5 grams and is intended for use on cats and small dogs up to 8 kg in weight. The large collar weighs 45 grams and is intended for use on dogs over 8 kg in weight. This risk assessment addresses exposure and risk associated with the use of flumethrin only; it does not address imidacloprid exposure associated with the use of the pet collar product.

The database of toxicology studies available for flumethrin provides a robust characterization of the hazard. There are no outstanding studies according to Part 158 data requirements for a non-food use pesticide registration. In addition, numerous studies from the scientific literature that describe the pharmacodynamic and pharmacokinetic profile of the pyrethroids in general have been considered in this assessment. This assessment is consistent with assessments performed for other pyrethroid pesticides.

Neurobehavioral changes characteristic of Type II pyrethroids (i.e., pawing, burrowing, salivation, and coarse tremors leading to choreoathetosis (CS-syndrome)) were observed at high doses in experimental toxicology studies with flumethrin. Although salivation was observed in multiple species and study durations, the decreased motor activity observed in the acute neurotoxicity (ACN) study was selected as the endpoint for risk assessment. Decreased motor activity was the most sensitive endpoint identified for flumethrin and is protective of the salivation seen throughout the database. Additional effects seen in one or more studies included hind-limb swelling, digit eating, and staining. Flumethrin also produced decreased body weights and food consumption in repeat dosing studies in rats at similar doses that produced decreased motor activity in the ACN.

One of the key elements in risk assessment is the appropriate integration of temporality between the exposure and hazard assessments. Following a single oral gavage dose, flumethrin is absorbed quickly in rats displaying decreased motor activity and increased salivation, neurotoxicity is observed within 5 hours, and rats recover within 24 hours without any persisting neurotoxic effects. This is generally consistent with the toxicity profiles for all the pyrethroids which are very similar and marked by rapid absorption, metabolism, and time-to-peak effect. The NOAELs and LOAELs established from flumethrin single dose and repeat dosing studies show that repeat exposures do not result in lower NOAELs. Thus, endpoints from single dose studies are considered protective of repeated exposure.

Evidence of increased qualitative or quantitative susceptibility of the offspring was not observed in any of the available animal testing guideline toxicity studies. However, the Agency will retain a 3X uncertainty factor to protect for exposures to children <6 years of age based on the following: 1) age-dependent pharmacokinetics, supported by rat Physiologically Based Pharmacokinetic (PBPK) model predictions of a 3-fold increase of pyrethroid concentration in juvenile brain compared to adults; 2) *in vitro* pharmacodynamic (PD) data and *in vivo* data

indicating similar responses between adult and juvenile rats at low doses; and 3) data indicating that the rat is a conservative model compared to the human based on species-specific pharmacodynamics of homologous sodium channel isoforms.

There were no treatment related increases in tumor incidences when compared to controls in both the rat chronic toxicity/carcinogenicity study and the carcinogenicity mouse study. In accordance with the Agency's 2005 Cancer Guidelines, there was no evidence of carcinogenicity in either species and this chemical is classified as "Not likely to be carcinogenic to humans."

There are no currently registered food uses for flumethrin; therefore, residue chemistry data are not required for flumethrin at this time. Additionally, a dietary exposure assessment was not conducted since there are no registered food uses and the registered pet collar use is not anticipated to result in drinking water exposures.

The residential exposure and risk estimates were calculated in this assessment to reflect chemical-specific exposure data in conjunction with exposure-specific data provided in the 2012 Residential SOPs. The chemical-specific exposure data submitted by the registrant was used to estimate exposure to pet collars assuming a 0.9971 liquid/0.0029 solid ratio (i.e., 99.71% liquid and 0.29% solid, the relative fraction of liquid and solid available for exposure). The residential handler exposures are not of concern for the small or large sized collars (i.e., total liquid/dust aggregate risk index (ARI) is ≥ 1) when assuming a liquid/dust ratio of 0.9971/0.0029). The ARIs range from 5.9 to 21. For the residential handler exposures, a total aggregated risk index (ARI) was used since the level of concern (LOCs) for dermal exposure (100) and inhalation exposure (30) are different. The residential post-application dermal exposure and risk estimates for adults are greater than the LOC (i.e., MOEs ≥ 100) for the small or large sized collars when assuming a liquid/dust ratio of 0.9971/0.0029. The residential post-application combined dermal and incidental oral exposure and risk estimates for children ($1 < 2$ years old) are greater than the LOC (i.e., MOEs ≥ 300) for the small or large sized collars when assuming a liquid/dust ratio of 0.9971/0.0029 ratio. Residential post-application inhalation exposure is expected to be negligible from pet collars; therefore, a quantitative assessment was not conducted.

A quantitative spray drift assessment was not conducted for the flumethrin pet collar since this use will not result in the potential for spray drift exposures.

There are currently no registered food uses for flumethrin and drinking water exposure is not expected from the registered pet collar uses of flumethrin; therefore, a quantitative aggregate risk assessment is not required at this time and HED has not made recommendations for residential exposure estimates to include in the aggregate assessment.

Occupational handler exposure to the flumethrin pet collar may occur via the dermal and inhalation route when placed on a cat or dog by a professional applicator/groomer. The occupational handler exposure resulted in no risk estimates of concern (ARIs ≥ 1) for the small or large sized collars when assuming a liquid/dust ratio of 0.9971/0.0029.

Occupational post-application exposure could potentially occur, however; these types of exposures are not expected to be greater than residential post-application exposures (i.e.,

minimal and infrequent contact by a professional animal care worker is expected to occur after a collar is applied). As a result, no quantitative occupational post-application exposure and risk assessment has been performed.

Restricted Entry Interval (REI)

The registered product does not fall within the scope of the Worker Protection Standards (WPS) for agricultural pesticides (i.e., plants on farms, forests, nurseries, or greenhouses) and therefore does not require an REI on the label.

Human Studies Review

This risk assessment relies in part on data from studies in which adult human subjects were intentionally exposed to a pesticide or other chemical. These data, which include the Residential SOPs (Treated Pets) and exposure data (MRIDs 48240140, 44433303, 44439901, 45519601, and 501408804) are (1) subject to ethics review pursuant to 40 CFR 26, (2) have received that review, and (3) are compliant with applicable ethics requirements. For certain studies, the ethics review may have included review by the Human Studies Review Board. Descriptions of data sources, as well as guidance on their use, can be found at the Agency website[1].

2.0 HED Recommendations

2.1 Data Deficiencies

No residue chemistry, occupational/residential exposure, or toxicology data deficiencies were identified.

2.2. Label Recommendations

2.2. Recommendations from Residential and Occupational Assessments

None.

3.0. Use Profile

Table 3.1 provides a summary of the registered uses of flumethrin.

Table 3.1. Summary of Directions for Use of Flumethrin.

Use Site		Formulation [EPA Reg. No.]	Application Rate	Use Directions and Limitations
Pet Collar Product				
	Small dogs and puppies (7		0.00124 lb ai/collar	Do not use on puppies under 7 weeks of age or

[1] [HYPERLINK "http://www2.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-handler-exposure-data"] and [HYPERLINK "http://www2.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-post-application-exposure"]

Table 3.1. Summary of Directions for Use of Flumethrin.				
Use Site		**Formulation [EPA Reg. No.]**	**Application Rate**	**Use Directions and Limitations**
Small Collar	weeks of age and older and up to 18 lbs body weight)	PNR 1427 Insecticide [EPA Reg. No. 11556-155] 4.5% flumethrin	(562.50 mg ai)	kittens under 10 weeks of age. The collar should be worn continuously for 8 months and replaced after 8 months for optimal protection.
	Cats and kittens (10 weeks of age and older)			
Large Collar	Large dogs and puppies (7 weeks of age and older and above 18 lbs body weight)		0.00446 lb ai/collar (2,023 mg ai)	

3.2 Anticipated Exposure Pathways

Humans are not exposed to flumethrin in food and drinking water since there are no currently registered food uses of flumethrin and drinking water exposure is not expected from the registered pet collar uses. Adults and children may be exposed to flumethrin in residential settings due to the currently registered uses. A quantitative spray drift assessment was not conducted for the flumethrin pet collar since this use will not result in the potential for spray drift exposures. Based on the registered use pattern for flumethrin, workers may be exposed to flumethrin while applying this pesticide. All these relevant exposure pathways have been included in this risk assessment.

3.3 Consideration of Environmental Justice

Potential areas of environmental justice concerns, to the extent possible, were considered in this human health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations," ([HYPERLINK "http://www.archives.gov/federal-register/executive-orders/pdf/12898.pdf"]). As a part of every pesticide risk assessment, OPP considers a large variety of consumer subgroups according to well-established procedures. In line with OPP policy, HED estimates risks to population subgroups from pesticide exposures that are based on patterns of that subgroup's food and water consumption, and activities in and around the home that involve pesticide use in a residential setting. Extensive data on food consumption patterns are compiled by the USDA under the NHANES/WWEIA and are used in pesticide risk assessments for all registered food uses of a pesticide. These data are analyzed and categorized by subgroups based on age and ethnic group. Additionally, OPP is able to assess dietary exposure to smaller, specialized subgroups and exposure assessments are performed when conditions or circumstances warrant. Whenever appropriate, non-dietary exposures based on home use of pesticide products and associated risks for adult applicators and for toddlers, youths, and adults entering or playing on treated areas post-application are evaluated. Further considerations are currently in development as OPP has committed resources and expertise to the

development of specialized software and models that consider exposure to bystanders and farm workers as well as lifestyle and traditional dietary patterns among specific subgroups.

4.0 Hazard Characterization and Dose-Response Assessment

Flumethrin is a member of the pyrethroid class of chemicals. Pyrethroids have historically been classified into two groups, Type I and Type II, based upon chemical structure and neurotoxicological effect. Type I pyrethroids, which lack an alpha-cyano moiety, induce in rats a syndrome consisting of aggressive sparring, altered sensitivity to external stimuli, and fine tremor progressing to whole-body tremor and prostration (T-syndrome). Type II pyrethroids, which contain an alpha-cyano moiety, in rats produce a syndrome that includes pawing, burrowing, salivation, and coarse tremors leading to choreoathetosis (CS-syndrome) [ADDIN EN.CITE
<EndNote><Cite><Author>Lawrence</Author><Year>1982</Year><RecNum>296</RecNum><DisplayText>(Verschoyle and Aldridge 1980; Lawrence and Casida 1982)</DisplayText><record><rec-number>296</rec-number><foreign-keys><key app="EN" db-id="et5pwxdw9wwrfre9zz4pesfuv952sssda2v2">296</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>LJ Lawrence</author><author>JE Casida</author></authors></contributors><titles><title>Pyrethroid toxicology: Mouse intracerebral sturcture-toxicity relationships</title><secondary-title>Pesticide Biochemistry and Physiology</secondary-title></titles><pages>9-14</pages><volume>18</volume><dates><year>1982</year></dates><urls></urls></record></Cite><Cite><Author>Verschoyle</Author><Year>1980</Year><RecNum>148</RecNum><record><rec-number>148</rec-number><foreign-keys><key app="EN" db-id="et5pwxdw9wwrfre9zz4pesfuv952sssda2v2">148</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Verschoyle, R. D.</author><author>Aldridge, W. N.</author></authors></contributors><titles><title>Structure-activity relationships of some pyrethroids in rats</title><secondary-title>Arch Toxicol</secondary-title></titles><pages>325-9</pages><volume>45</volume><number>4</number><edition>1980/10/01</edition><keywords><keyword>Animals</keyword><keyword>Behavior, Animal/drug effects</keyword><keyword>Female</keyword><keyword>Injections, Intravenous</keyword><keyword>Pyrethrins/*toxicity</keyword><keyword>Rats</keyword><keyword>Stereoisomerism</keyword><keyword>Structure-Activity Relationship</keyword></keywords><dates><year>1980</year><pub-dates><date>Oct</date></pub-dates></dates><isbn>0340-5761 (Print)</isbn><accession-num>7447703</accession-num><urls><related-urls><url>http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=7447703</url></related-urls></urls><language>eng</language></record></Cite></EndNote>]. Flumethrin is a Type II synthetic pyrethroid. The adverse outcome pathway (AOP) shared by pyrethroids involves the ability to interact with voltage-gated sodium channels (VGSCs) in the central and peripheral nervous system, leading to changes in neuron firing, and ultimately neurotoxicity (see Figure 1).

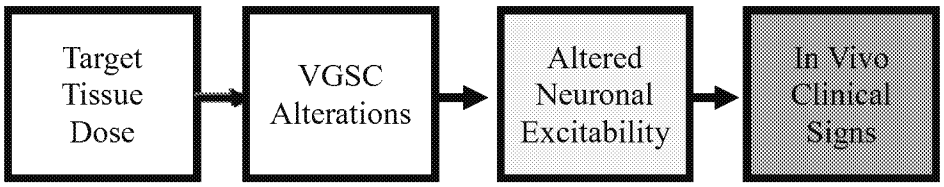

Figure 1. Adverse outcome pathway for pyrethroids

4.1 Toxicology Studies Available for Analysis

The database of experimental toxicology studies available for flumethrin provides a robust characterization of the hazard potential for children 6 years old and older and for adults. There are no outstanding studies according to Part 158 data requirements for a non-food use pesticide registration. However, there are on-going efforts to develop data to inform the potential sensitivity of infants and younger children to pyrethroids as a class which is discussed further in Section 4.4. Despite these scientific efforts, HED is confident that it has chosen points of departure and uncertainty factors in this risk assessment which are health protective and have a strong scientific foundation.

The data from the following studies were used to evaluate the hazard potential of flumethrin:

-Developmental Rat Studies
-Developmental Rabbit Studies
-Reproduction Rat Study
-Chronic/Cancer Mouse Study
-Chronic/Cancer Rat Study
-28 Day Mouse Study
-90- Day Rat and Mouse Study
-Acute Neurotoxicity (ACN) Rat Study
-Subchronic Neurotoxicity (SCN) Rat Study
-Developmental Neurotoxicity (DNT) Rat Study
-14-day, 28-day, and 90-day Dermal Rat Study
-28-day Inhalation Rat Study
-Genotoxicity Studies
-Immunotoxicity Study
-Metabolism and Pharmacokinetics

The studies available for consideration of flumethrin toxicity provide a comprehensive database. In addition, numerous studies from the scientific literature conducted over several decades describe the pharmacodynamic and pharmacokinetic profile of the pyrethroids in general; this scientific literature has been recently reviewed by several groups [ADDIN EN.CITE ADDIN EN.CITE.DATA]. Although none of this literature provides any specific data on flumethrin, because of the shared toxicological properties of the members of this class of pesticides, these studies are informative in the hazard characterization of flumethrin.

4.2 Flumethrin Toxicological Profile

Flumethrin has been evaluated for a variety of toxic effects in guideline experimental toxicity studies. Neurobehavioral changes characteristic of Type II pyrethroids (e.g., pawing, burrowing, salivation, and coarse tremors leading to choreoathetosis (CS-syndrome)) were observed at high doses in experimental toxicology studies with flumethrin. Although salivation was observed in nearly all experimental studies in all species and durations, decreased motor activity was observed at lower doses in the ACN study and thus it was selected as the endpoint for risk assessment. Additional effects seen in one or more studies included hind-limb swelling, digit eating, and staining. Flumethrin also produced decreased body weights, and food consumption in repeat dosing studies at similar doses that produced decreased motor activity in the ACN study. Regarding gender, males were found to be more sensitive throughout the database.

In a multi-generation reproduction study in the rat, parental toxicity was expressed as reductions in pituitary weights (F1 generation) for males at the low dose and reduction in liver weights in females (F0 and F1 generations) at the mid-dose. Offspring toxicity was expressed by decreased body weight, decreased rearing indexes, and deaths at post-natal days 0-4, all occurring at a dose over 2 times higher than the dose eliciting decreased motor activity. Developmental effects were observed in both rat and rabbit developmental studies (delayed ossification, microphthalmia) but these effects occurred at doses equal to or higher than the maternal effects. Maternal effects (such as decreased body weight and decreased urine) occurred at doses 2 times higher than the dose eliciting decreased motor activity.

The pharmacokinetics of flumethrin is similar to other pyrethroids (i.e., rapid absorption and clearance). Following a single oral dose, flumethrin was excreted mainly via the feces (68%) within 24 hours. In radiolabeled flumethrin studies, absorbed radioactivity calculated as the sum of urine, bile, and body tissues accounts for 75% of the given dose in bile duct-cannulated rats, indicating a high level of absorption following an oral dose. The rapid absorption was also observed in an exploratory pharmacokinetic (PK) study where the maximum plasma levels of flumethrin were found at 2 and 4 hours after administration for each dose level, respectively.

The acute toxicity profile of flumethrin consists of mild toxicity via the oral, dermal, and inhalation routes of exposure (Toxicity Category II). The eye irritation study indicates that the technical is an amorphous glass-like solid that does not exist as a fine powder at room temperature and so cannot be tested by this exposure route. A waiver was granted for the eye irritation study with assignment to toxicity category IV by this exposure route. Flumethrin was assigned to Toxicity Category IV as a skin irritant and it is not a dermal sensitizer.

4.2.1 Critical Duration of Exposure

One of the key elements in risk assessment is the appropriate integration of temporality between the exposure and hazard assessments. Following a single oral gavage dose, flumethrin is absorbed quickly in rats displaying decreased motor activity and increased salivation; neurotoxicity is observed within 5 hours, and rats recover within 24 hours without any persisting neurotoxic effects. This is generally consistent with the toxicity profiles for all the pyrethroids which are very similar and marked by rapid absorption, metabolism, and time-to-peak effect. The NOAELs and LOAELs for both motor activity changes and decreases in body weight established from results of experimental toxicity studies with flumethrin are remarkably consistent across durations of exposure ranging from a single dose up to 2-years of dosing (see Table 4.3).

Table 4.3: Experimental Toxicology Studies with Similar Results

Study	Duration	Study findings (mg/kg/day)	
Acute Neurotoxicity	Acute, single exposure	NOAEL = 0.5	LOAEL = 1.0
Developmental neurotoxicity	86 days	NOAEL = 1.0	LOAEL = 2.0
Sub-chronic mouse	90 day	NOAEL = 0.9	LOAEL = 1.4
Sub-chronic rat	90 day	NOAEL = 0.7	LOAEL = 2.9
Sub-chronic neurotoxicity	90 day	NOAEL = 1.0	LOAEL = 2.6
Reproductive toxicity	120 days	NOAEL = 0.2	LOAEL = 2.4
Chronic-carcinogenicity rat	2-year	NOAEL = 0.7	LOAEL = 2.0
Carcinogenicity mouse	2-year	NOAEL = 0.4	LOAEL = 2.0

Looking at the NOAELs and LOAELs established from flumethrin single dose and repeat dosing studies it is apparent that repeat exposures do not result in lower NOAELs. This is consistent with the general kinetic profile for the pyrethroids. The LOAEL from the ACN (1.0 mg/kg) is similar to the LOAEL from the chronic 2-year cancer study (2.0 mg/kg/day). Therefore, the endpoint from the acute study is protective of the endpoints from the repeat dosing studies. Thus for purposes of endpoint selection and exposure assessment, only single day risk assessments need to be conducted.

4.3. Pyrethroid Pharmacokinetic and Pharmacodynamic Profile

The extensive body of scientific literature on the pyrethroids provides a unique insight into the contributions of PK and pharmacodynamics (PD) to the general toxicity profile of this class of chemicals. This information also provides valuable insight into the potential age-related differences in toxicity for the pyrethroids. The following sections discuss the specific issues related to pyrethroid PK, PD, and age-related differences in pyrethroid toxicity.

4.3.1 Pharmacokinetics

Pharmacokinetics can be defined as what the body does to the chemical; in this case, how pyrethroids are distributed and eliminated following exposure. Specific to pyrethroids, PK refers to the process(es) which determine the concentration of the pyrethroids reaching sodium channels. The underlying pharmacokinetics of pyrethroids is an important determinant of their

toxicity because the concentration of pyrethroid at the sodium channel relates to the extent of toxicity; greater pyrethroid concentration translates as increased neurotoxicity. Two physiological processes that significantly contribute to the PK include metabolism and partitioning. Carboxylesterases and P450 enzymes are the two major enzyme families responsible for metabolism of pyrethroids. It is the ontogeny of these enzymes that accounts for the age-related sensitivity observed after pyrethroid exposures. With respect to the partitioning of pyrethroids within the body, pyrethroids are highly lipophilic and preferentially deposit in fatty tissue such as adipose compared to leaner tissues such as muscle. Pyrethroid residues in fatty tissue are not available to interact with the VGSCs in vital tissues and therefore do not contribute to overall toxicity.

Physiologically-based pharmacokinetic (PBPK) models, designed to predict pyrethroid concentration in tissues following *in vivo* exposure, have recently been developed by the Agency. The Agency has determined that the important PK properties relevant for the metabolism and distribution of pyrethroids in the body are sufficiently similar for members of this class such that using a 'generic' or family model structure for this class is scientifically appropriate. In other words, due to the similarities in the PK profiles of pyrethroids, a single model structure is able to predict the tissue dose based on the pharmacokinetics of every member of the class. The family modeling approach was presented to and supported by the FIFRA SAP [ADDIN EN.CITE <EndNote><Cite><Author>USEPA</Author><Year>2007</Year><RecNum>561</RecNum><DisplayText>(USEPA 2007)</DisplayText><record><rec-number>561</rec-number><foreign-keys><key app="EN" db-id="et5pwxdw9wwrfre9zz4pesfuv952sssda2v2">561</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>USEPA</author></authors></contributors><titles><title>Meeting Minutes: FIFRA SAP Meeting on Assessing Approaches for the Development of PBPK Models of Pyrethroid Pesticides. Document ID: EPA-HQ-OPP-2007-0388-0049. www.regulations.gov</title></titles><dates><year>2007</year></dates><urls></urls></record></Cite></EndNote>].

In 2011 the Agency conducted an analysis of the toxicokinetic profile of pyrethroids as a class. Several studies in this analysis indicate that there are age-dependent PK differences for the pyrethroids (i.e., there are differences in the ability of adults and juveniles to metabolize pyrethroids). The enzymes which metabolize and detoxify the pyrethroids are present in rats and humans at birth [ADDIN EN.CITE ADDIN EN.CITE.DATA]. As a result, both juveniles and adults are able to tolerate low doses of pyrethroids when the internal dose, or the amount of pyrethroid at the sodium channel, is low. However, the activity of these enzymes increases with age, conveying in adults a greater capacity to detoxify pyrethroids compared to juveniles [ADDIN EN.CITE ADDIN EN.CITE.DATA]. For example, the rate of *in vitro* metabolism of deltamethrin by plasma carboxyesterases, hepatic carboxyesterases, and hepatic microsomes are at least 6 times higher for PND 90 rats compared to PND 10 rats [ADDIN EN.CITE <EndNote><Cite><Author>Anand</Author><Year>2006</Year><RecNum>147</RecNum><DisplayText>(Anand et. al. 2006)</DisplayText><record><rec-number>147</rec-number><foreign-keys><key app="EN" db-id="et5pwxdw9wwrfre9zz4pesfuv952sssda2v2">147</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Anand, Sathanandam

S.</author><author>Bruckner, James V.</author><author>Haines, Wendy T.</author><author>Muralidhara, Srinivasa</author><author>Fisher, Jeffrey W.</author><author>Padilla, Stephanie</author></authors></contributors><titles><title>Characterization of deltamethrin metabolism by rat plasma and liver microsomes</title><secondary-title>Toxicology and Applied Pharmacology</secondary-title></titles><pages>156-166</pages><volume>212</volume><number>2</number><keywords><keyword>Carboxylesterases</keyword><keyword>CYP450s</keyword><keyword>Deltamethrin</keyword><keyword>Pyrethroid metabolism</keyword><keyword>Liver microsomes</keyword><keyword>Plasma</keyword><keyword>Vmax and Km</keyword><keyword>Rat</keyword></keywords><dates><year>2006</year></dates><isbn>0041-008X</isbn><urls><related-urls><url>http://www.sciencedirect.com/science/article/B6WXH-4H45GTM-1/2/ef2038f2560398715f630d868e5a89f5</url></related-urls></urls></record></Cite></EndNote>]. As a consequence, higher internal doses (i.e., those associated with high doses in experimental toxicology studies) overwhelm the clearance mechanisms in juveniles but because adults have greater enzyme activity, they are able to tolerate higher doses prior to the onset of toxicity. As a matter of perspective, the anticipated exposures from typical dietary or residential activities are not expected to overwhelm the premature metabolic systems in juveniles.

Predictive PBPK models have recently been developed to describe the PK of a few pyrethroids [ADDIN EN.CITE <EndNote><Cite><Author>Godin</Author><Year>2010</Year><RecNum>542</RecNum><DisplayText>(Mirfazaelian et. al. 2006; Godin et. al. 2010)</DisplayText><record><rec-number>542</rec-number><foreign-keys><key app="EN" db-id="et5pwxdw9wwrfre9zz4pesfuv952sssda2v2">542</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Godin, Stephen J.</author><author>DeVito, Michael J.</author><author>Hughes, Michael F.</author><author>Ross, David G.</author><author>Scollon, Edward J.</author><author>Starr, James M.</author><author>Setzer, R. Woodrow</author><author>Conolly, Rory B.</author><author>Tornero-Velez, Rogelio</author></authors></contributors><titles><title>Physiologically Based Pharmacokinetic Modeling of Deltamethrin: Development of a Rat and Human Diffusion-Limited Model</title><secondary-title>Toxicol. Sci.</secondary-title></titles><pages>330-343</pages><volume>115</volume><number>2</number><dates><year>2010</year><pub-dates><date>June 1, 2010</date></pub-dates></dates><urls><related-urls><url>http://toxsci.oxfordjournals.org/cgi/content/abstract/115/2/330</url></related-urls></urls><electronic-resource-num>10.1093/toxsci/kfq051</electronic-resource-num></record></Cite><Cite><Author>Mirfazaelian</Author><Year>2006</Year><RecNum>477</RecNum><record><rec-number>477</rec-number><foreign-keys><key app="EN" db-id="et5pwxdw9wwrfre9zz4pesfuv952sssda2v2">477</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Mirfazaelian, A</author><author>Kim, KB</author><author>Anand, SS</author><author>Kim, HJ</author><author>Tornero-Velez, R</author><author>Bruckner, JV</author><author>Fisher, JW</author></authors></contributors><titles><title>Development

of a physiologically based pharmacokinetic model for deltamethrin in the adult male Sprague-Dawley rat</title><secondary-title>Toxicol Sci</secondary-title></titles><pages>432 - 442</pages><volume>93</volume><number>2</number><dates><year>2006</year></dates> <urls></urls></record></Cite></EndNote>]. Among these is an age-dependent model developed by the Agency which is capable of predicting the concentration of deltamethrin in the brains of rats at multiple ages [ADDIN EN.CITE <EndNote><Cite><Author>Tornero-Velez</Author><Year>2010</Year><RecNum>541</RecNum><DisplayText>(Tornero-Velez et. al. 2010)</DisplayText><record><rec-number>541</rec-number><foreign-keys><key app="EN" db-id="et5pwxdw9wwrfre9zz4pesfuv952sssda2v2">541</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Rogelio Tornero-Velez</author><author>Ahmad Mirfazaelian</author><author>Kyu-Bong Kim</author><author>Sathanandam S. Anand</author><author>Hyo J. Kim</author><author>Wendy T. Haines</author><author>James V, Bruckner</author><author>Jeffrey W. Fisher</author></authors></contributors><titles><title>Evaluation of deltamethrin kinetics and dosimetry in the maturing rat using a PBPK model</title><secondary-title>Toxicol Appl Pharmacol</secondary-title></titles><periodical><full-title>Toxicol Appl Pharmacol</full-title></periodical><pages>208-17</pages><volume>244</volume><dates><year>2010</year></dates><urls></urls></record> </Cite></EndNote>]. The brain is considered the primary target organ for pyrethroids and increased pyrethroid concentrations are correlated with increasing systemic toxicity. This model predicts that, compared to adult rats (i.e., 90-days old), equivalent brain concentrations of deltamethrin would be achieved with a 3.8X fold lower oral dose in 10-day old rats and 2.5X lower dose in 21-day old rats [ADDIN EN.CITE <EndNote><Cite><Author>Tornero-Velez</Author><Year>2010</Year><RecNum>541</RecNum><DisplayText>(Tornero-Velez et. al. 2010)</DisplayText><record><rec-number>541</rec-number><foreign-keys><key app="EN" db-id="et5pwxdw9wwrfre9zz4pesfuv952sssda2v2">541</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Rogelio Tornero-Velez</author><author>Ahmad Mirfazaelian</author><author>Kyu-Bong Kim</author><author>Sathanandam S. Anand</author><author>Hyo J. Kim</author><author>Wendy T. Haines</author><author>James V, Bruckner</author><author>Jeffrey W. Fisher</author></authors></contributors><titles><title>Evaluation of deltamethrin kinetics and dosimetry in the maturing rat using a PBPK model</title><secondary-title>Toxicol Appl Pharmacol</secondary-title></titles><periodical><full-title>Toxicol Appl Pharmacol</full-title></periodical><pages>208-17</pages><volume>244</volume><dates><year>2010</year></dates><urls></urls></record> </Cite></EndNote>]. For example, a 1 mg/kg dose in the adult is equivalent to a 0.26 mg/kg dose (≈1 mg/kg÷3.8mg/kg) in the 10-day old rats and to a 0.4 mg/kg (≈1 mg/kg÷2.5mg/kg) dose in a 21-day old rat. The difference between a 3.8- and a 2.5-fold dose is within background variability of the model. As a result, the Agency concludes that juvenile rats are 3X more sensitive than adults with respect to pyrethroid PK.

4.3.2 Pharmacodynamics

Pharmacodynamics (PD) can be defined as the changes that chemicals cause to the body, in this case, how pyrethroids interact with the sodium channels. Substantial evidence from *in vitro* and

in vivo studies support the AOP illustrated in Figure 1 above as well as disruption of sodium channels by pyrethroids as an early key event in this AOP [ADDIN EN.CITE ADDIN EN.CITE.DATA]. As a new active ingredient, there are no recent studies for flumethrin which provide information on how flumethrin interacts with the sodium channels. However, there are several recent studies which provide information on a variety of other pyrethroids. Choi and Soderlund [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Choi</Author><Year>2006</Year><RecNum>17</RecNum><DisplayText>(2006)</DisplayText><record><rec-number>17</rec-number><foreign-keys><key app="EN" db-id="et5pwxdw9wwrfre9zz4pesfuv952sssda2v2">17</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Choi, Jin-Sung</author><author>Soderlund, David M.</author></authors></contributors><titles><title>Structure-activity relationships for the action of 11 pyrethroid insecticides on rat Nav1.8 sodium channels expressed in Xenopus oocytes</title><secondary-title>Toxicology and Applied Pharmacology</secondary-title></titles><periodical><full-title>Toxicology and Applied Pharmacology</full-title></periodical><pages>233-244</pages><volume>211</volume><number>3</number><keywords><keyword>Allethrin</keyword><keyword>Bifenthrin</keyword><keyword>Cismethrin</keyword><keyword>Cyfluthrin</keyword><keyword>Cyhalothrin</keyword><keyword>Cypermethrin</keyword><keyword>Deltamethrin</keyword><keyword>Fenpropathrin</keyword><keyword>Fenvalerate</keyword><keyword>Permethrin</keyword><keyword>Tefluthrin</keyword><keyword>Pyrethroid</keyword><keyword>sodium channel</keyword></keywords><dates><year>2006</year><pub-dates><date>2006/3/15</date></pub-dates></dates><label>common MOA</label><urls><related-urls><url>http://www.sciencedirect.com/science/article/B6WXH-4GR33KN-1/1/7ebec668266c1bf88d0a347e2ddef4d1</url></related-urls></urls></record></Cite></EndNote>] examined interactions of several pyrethroids with mammalian VGSCs expressed in *Xenopus* oocytes. With respect to altered neuronal excitability, Type I pyrethroids cause slight prolongations of the sodium current tails (e.g. ~20 ms), often resulting in long trains of action potentials. In contrast, Type II pyrethroids significantly prolong sodium current tails (e.g. 200ms to minutes) typically resulting in increased resting membrane potential and ultimately causing depolarization dependent action potential block. Cao et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Cao</Author><Year>2011</Year><RecNum>671</RecNum><DisplayText>(2011a)</DisplayText><record><rec-number>671</rec-number><foreign-keys><key app="EN" db-id="et5pwxdw9wwrfre9zz4pesfuv952sssda2v2">671</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Cao, Z.</author><author>Shafer, T. J.</author><author>Crofton, K. M.</author><author>Gennings, C.</author><author>Murray, T. F.</author></authors></contributors><auth-address>University of California, Davis.</auth-address><titles><title>Additivity of Pyrethroid Actions on Sodium Influx in Cerebrocortical Neurons in Primary Culture</title><secondary-title>Environ Health Perspect</secondary-title></titles><periodical><full-title>Environ Health Perspect</full-title></periodical><edition>2011/06/15</edition><dates><year>2011</year><pub-dates><date>Jun 10</date></pub-dates></dates><isbn>1552-9924 (Electronic)
0091-6765 (Linking)</isbn><accession-num>21665567</accession-num><urls><related-urls><url>http://www.ncbi.nlm.nih.gov/pubmed/21665567</url></related-

urls></urls><electronic-resource-num>10.1289/ehp.1003394</electronic-resource-num><language>Eng</language></record></Cite></EndNote>] measured Na influx in primary cultures of mammalian (mouse) neurons and demonstrated that pyrethroids caused increases in Na influx in this model; this confirms the ability of pyrethroids to interact with VGSC in intact mammalian neurons. An additional study by Cao et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Cao</Author><Year>2011</Year><RecNum>672</RecNum><DisplayText>(2011b)</DisplayText><record><rec-number>672</rec-number><foreign-keys><key app="EN" db-id="et5pwxdw9wwrfre9zz4pesfuv952sssda2v2">672</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Zhengyu Cao</author><author>Timothy J. Shafer</author><author>Thomas F. Murry</author></authors></contributors><titles><title>Mechanisms of Pyrethroid Insecticide-Induced Stimulation of Calcium Influx in Neocortical Neurons</title><secondary-title>J Pharmacology and Experimental Therapy</secondary-title></titles><periodical><full-title>J Pharmacology and Experimental Therapy</full-title></periodical><pages>197-205</pages><volume>336</volume><number>1</number><dates><year>2011</year></dates><urls></urls></record></Cite></EndNote>] demonstrated that the interaction of pyrethroids with VGSC caused changes in neuronal excitability that resulted in calcium influx into intact mouse neurons.

HED would prefer to use an early key event in the AOP for pyrethroids in selection of points of departure. However, *in vivo* techniques used to detect VGSC alteration and altered neuronal excitability are not practical for use in risk assessment at this time and approaches for extrapolating *in vitro* findings to *in vivo* measures are not yet developed. As such, the Agency is focusing its efforts for all pyrethroids in hazard characterization and identification on the apical endpoint (i.e., changes in neurobehavior in laboratory animals). Neurotoxicity resulting from pyrethroids are generally characterized by tremors, hyper- or hypothermia, heightened response to stimuli, salivation, tremors and convulsions [ADDIN EN.CITE ADDIN EN.CITE.DATA].

In contrast to the age-related PK differences identified in the 2011 analysis, PD contributions to pyrethroid toxicity are not age-dependent even though there are several variations of sodium channels, called isoforms, which are differentially expressed by tissue and age. Due to the nature of the interaction of pyrethroids with sodium channels, it is difficult to obtain dynamic information *in vivo.* To date, a readily useable biomarker of *in vivo* pyrethroid interaction with sodium channels has not been identified, making it impractical to determine the isoform combinations that are present and being acted upon by pyrethroids. Therefore, much of the information available to the Agency to characterize the PD relationship between pyrethroids and sodium channels has been derived from *in vitro* studies using frog oocytes or nervous cells artificially grown in media. While these *in vitro* techniques do not provide direct quantitative measure of *in vivo* pyrethroid activity, they consistently and qualitatively demonstrate that channel isoforms expressed in juveniles are not more sensitive to pyrethroid perturbation compared to isoforms expressed in adults and that, pharmacodynamically, the rat is a conservative model for humans. For example, Meacham et al. [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Meacham</Author><Year>2008</Year><RecNum>29</RecNum>

<DisplayText>(2008)</DisplayText><record><rec-number>29</rec-number><foreign-keys><key app="EN" db-id="et5pwxdw9wwrfre9zz4pesfuv952sssda2v2">29</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Meacham, Connie A.</author><author>Brodfuehrer, Peter D.</author><author>Watkins, Jennifer A.</author><author>Shafer, Timothy J.</author></authors></contributors><titles><title>Developmentally-regulated sodium channel subunits are differentially sensitive to [alpha]-cyano containing pyrethroids</title><secondary-title>Toxicology and Applied Pharmacology</secondary-title></titles><pages>273-81</pages><volume>231</volume><keywords><keyword>Pyrethroid</keyword><keyword>Sodium channel</keyword><keyword>Development</keyword><keyword>Deltamethrin</keyword></keywords><dates><year>2008</year></dates><label>channel</label><urls><related-urls><url>http://www.sciencedirect.com/science/article/B6WXH-4SD29K9-4/1/73d476e0ea7a741bd7ae5227ae449b63</url></related-urls></urls></record></Cite></EndNote>], compared the sensitivity of an adult isoform and a juvenile isoform expressed in frog oocytes to deltamethrin. The isoforms had comparable responses at environmentally relevant concentrations (<500 nM) of deltamethrin, suggesting a lack of PD difference between juveniles and adults at low exposure levels. In addition, in a direct comparison of a homologous rat and human VGSC isoform, NaV1.3, Tan and Soderlund, [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Tan</Author><Year>2009</Year><RecNum>100</RecNum><DisplayText>(2009)</DisplayText><record><rec-number>100</rec-number><foreign-keys><key app="EN" db-id="et5pwxdw9wwrfre9zz4pesfuv952sssda2v2">100</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Tan, Jianguo</author><author>Soderlund, David M.</author></authors></contributors><titles><title>Human and rat Nav1.3 voltage-gated sodium channels differ in inactivation properties and sensitivity to the pyrethroid insecticide tefluthrin</title><secondary-title>NeuroToxicology</secondary-title></titles><periodical><full-title>Neurotoxicology</full-title></periodical><pages>81-89</pages><volume>30</volume><number>1</number><keywords><keyword>Nav1.3</keyword><keyword>Oocyte</keyword><keyword>Sodium channel</keyword><keyword>Pyrethroid</keyword><keyword>Tefluthrin</keyword><keyword>Rat</keyword><keyword>Human</keyword></keywords><dates><year>2009</year></dates><isbn>0161-813X</isbn><urls><related-urls><url>http://www.sciencedirect.com/science/article/B6W81-4TVHSG8-1/2/ce978734793cea869e6a583ba507194c</url></related-urls></urls></record></Cite></EndNote>] found the rat isoform was 4-fold more sensitive than the equivalent human sodium channel to the pyrethroid tefluthrin [ADDIN EN.CITE <EndNote><Cite><Author>Tan</Author><Year>2009</Year><RecNum>100</RecNum><DisplayText>(Tan and Soderlund 2009)</DisplayText><record><rec-number>100</rec-number><foreign-keys><key app="EN" db-id="et5pwxdw9wwrfre9zz4pesfuv952sssda2v2">100</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Tan, Jianguo</author><author>Soderlund, David M.</author></authors></contributors><titles><title>Human and rat Nav1.3 voltage-gated sodium channels differ in inactivation properties and sensitivity to the pyrethroid insecticide

tefluthrin</title><secondary-title>NeuroToxicology</secondary-title></titles><periodical><full-title>Neurotoxicology</full-title></periodical><pages>81-89</pages><volume>30</volume><number>1</number><keywords><keyword>Nav1.3</keyword><keyword>Oocyte</keyword><keyword>Sodium channel</keyword><keyword>Pyrethroid</keyword><keyword>Tefluthrin</keyword><keyword>Rat</keyword><keyword>Human</keyword></keywords><dates><year>2009</year></dates><isbn>0161-813X</isbn><urls><related-urls><url>http://www.sciencedirect.com/science/article/B6W81-4TVHSG8-1/2/ce978734793cea869e6a583ba507194c</url></related-urls></urls></record></Cite></EndNote>], suggesting the rat is a highly sensitive model and extrapolations from the rat would be protective of human health. The occurrence and ontogeny of voltage-gated sodium channels in humans is not well characterized compared to the rat. However, based on the comparable function and distribution of sodium channels between the species, the rat is an appropriate surrogate for the evaluation of human PD [ADDIN EN.CITE <EndNote><Cite><Author>Goldin</Author><Year>2000</Year><RecNum>566</RecNum><DisplayText>(Goldin et. al. 2000; Goldin 2002)</DisplayText><record><rec-number>566</rec-number><foreign-keys><key app="EN" db-id="et5pwxdw9wwrfre9zz4pesfuv952sssda2v2">566</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>AL Goldin</author><author>RL Barchi</author><author>JH Caldwell</author><author>F Hofmann</author><author>JR Howe</author><author>JC Hunter</author><author>RG Kallen</author><author>G Mandel</author><author>MH Meisler</author><author>YBNetter</author><author>M Noda</author><author>MM Tamkun</author><author>SG Waxman</author><author>JN Wood</author><author>WA Catterall</author></authors></contributors><titles><title>Nomenclature of voltage-gated sodium channels</title><secondary-title>neuron</secondary-title></titles><pages>365-8</pages><volume>28</volume><number>2</number><dates><year>2000</year></dates><urls></urls></record></Cite><Cite><Author>Goldin</Author><Year>2002</Year><RecNum>419</RecNum><record><rec-number>419</rec-number><foreign-keys><key app="EN" db-id="et5pwxdw9wwrfre9zz4pesfuv952sssda2v2">419</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Goldin, Alan L.</author></authors></contributors><titles><title>Evolution of voltage-gated Na+ channels</title><secondary-title>J Exp Biol</secondary-title></titles><pages>575-584</pages><volume>205</volume><number>5</number><dates><year>2002</year><pub-dates><date>March 1, 2002</date></pub-dates></dates><urls><related-urls><url>http://jeb.biologists.org/cgi/content/abstract/205/5/575</url></related-urls></urls></record></Cite></EndNote>]. As a result, the Agency concludes that juvenile rats are not more sensitive than adults with respect to pyrethroid pharmacodynamics.

4.4 Consideration of Toxicity to Children

The Agency will retain a 3X uncertainty factor to protect for exposures to children <6 years of age based on the increased quantitative susceptibility seen in the scientific literature related to pyrethroid pharmacokinetics. This is consistent with the Agency's 2011 analysis and is supported by rat PBPK model predictions of a 3-fold increase of deltamethrin concentrations in the juvenile brain compared to adults (see Section 4.3.1). The PK of pyrethroids as a group is sufficiently similar that significant deviations from the 3-fold increase of deltamethrin

concentrations are not expected for other pyrethroids. As noted in Section 4.3.2, juveniles are not more sensitive than adults with respect to pyrethroid pharmacodynamics and thus no uncertainty factor is needed for PD considerations.

4.4.1 Completeness of the Toxicology Database

The flumethrin toxicological database is sufficient for risk assessment purposes. Flumethrin has all of the required toxicity studies to assess the current non-food use.

4.4.2 Evidence of Neurotoxicity

There are no residual uncertainties for flumethrin with regard to evidence of neurotoxicity. Flumethrin, like other pyrethroids, causes neurotoxicity from interaction with sodium channels leading to clinical signs of neurotoxicity. Neurotoxicity was consistently observed throughout the database in a dose-dependent manner in most all of the studies conducted. The mode of action is fully characterized and selected endpoints are protective of these neurotoxic effects.

4.4.3 Evidence of Sensitivity/Susceptibility in the Developing or Young Animal

Based on the flumethrin-specific data and the extensive body of peer-reviewed literature on pyrethroids available, the Agency reached a number of conclusions including the following:

- The Agency has no residual uncertainties regarding age related sensitivities for women of child bearing age as well as for all adult populations and children > 6 years of age, based on the absence of pre-natal sensitivity observed in 76 guideline studies for 24 pyrethroids, the scientific literature, and the flumethrin guideline toxicological studies.
- Although the flumethrin toxicological database was not considered in the 2011 analysis, the flumethrin developmental, reproductive, and DNT toxicity studies are consistent with other members of the pyrethroid class in that no evidence of increased quantitative or qualitative susceptibility was observed in these studies.
- No evidence of increased quantitative or qualitative susceptibility was seen in the pyrethroid scientific literature related to pharmacodynamics.
- The Agency will retain a 3X uncertainty factor to protect for exposures to children <6 years of age based on the increased quantitative susceptibility seen in the scientific literature related to pyrethroid pharmacokinetics.

The Agency is aware that additional *in vitro* and *in vivo* studies are currently being conducted that could potentially inform a number of issues related to pyrethroid toxicity as a class. In 2010, the Agency requested proposals for study protocols which could identify and quantify potential juvenile sensitivity and received a single, coordinated response from the Pyrethrin and Pyrethroids Working Group (PPTWG), a conglomerate of pyrethroid registrants. The PPTWG protocol was reviewed during a July 2010 FIFRA SAP meeting[2]. Based on comments from the SAP, the initial study proposal was refined. At present time, pesticide registrants and product formulators have come together as Council for the Advancement of Pyrethroid Human Risk Assessment (CAPHRA) and plan on doing the following: 1) conducting *in vitro* studies

[2] http://www.epa.gov/scipoly/sap/meetings/2010/072310meeting.html

demonstrating the interaction of pyrethroids exogenously expressed rat and human VGSCs in *Xenopus* oocytes; 2) conducting *in vitro* studies demonstrating interaction of pyrethroids in rat neurolemma cells; 3) developing rat and human PBPK models, including additional pharmacokinetic data; and 4) conducting *in vivo* behavioral testing using auditory startle testing in rats. As these data becomes available, the Agency will determine whether re-evaluation of the age-related sensitivity of pyrethroids is appropriate.

4.4.4 Residual Uncertainty in the Exposure Database

There are no residual uncertainties with regard to residential exposure. The residential exposure assessment is based on conservative, health-protective assumptions that ensure that exposures to the proposed flumethrin uses are not underestimated. There are no anticipated dietary (food and drinking water) exposures based on the registered uses of flumethrin.

4.5 Toxicity Endpoint and Point of Departure Selections

4.5.1 Dose-Response Assessment

The details for selecting toxicity endpoints and points of departure (PODs) are presented in Appendix A2. Based on the registered use pattern for flumethrin, the exposure profiles are dermal, inhalation, and incidental oral exposures. Because of the non-food use of flumethrin, dietary endpoints were not established.

Dietary Endpoints: Registered uses for flumethrin are non-food uses. Acute or chronic dietary PODs have not been established for this risk assessment.

Short-term Dermal: Quantification of dermal risks was performed using a route-specific 90-day dermal rat study with a NOAEL of 10 mg/kg/day and a LOAEL of 30 mg/kg/day based on loss of hair; decreased body weight and body weight gain (males); decreased erythrocytes; high stepping gait; and increased absolute spleen weight. The high stepping gait is considered suggestive of neurotoxicity.

Short-term Incidental Oral: Quantification of incidental oral ingestion risks was performed using the rat acute neurotoxicity study with a NOAEL of 0.5 mg/kg/day and a LOAEL of 1 mg/kg/day based on decreased motor/locomotor activity; increased staining of the mouth, perianal, and nose regions; increased lacrimation; and increased salivation. This endpoint is appropriate for the exposure scenario because repeat exposures do not result in lower NOAELs for flumethrin (see section 4.2.1).

Short-term Inhalation: Quantification of inhalation risks was performed using the subchronic inhalation study with a NOAEL of 0.12 mg/m^3 and a LOAEL of 1.33 mg /m^3 based on clinical signs of neurotoxicity.

The methods and dosimetry equations described in EPA's reference concentration (RfC) guidance (1994) are suited for calculating human equivalent concentrations (HECs) based on the inhalation toxicity point of departure (NOAEL, LOAEL, or BMDL) for use in MOE calculations. The regional-deposited-dose ratio (RDDR), which accounts for the particulate

diameter (mass median aerodynamic diameter [MMAD] and geometric standard deviation [σ_g] of aerosols), can be used to estimate the different dose fractions deposited along the respiratory tract. The RDDR is also based on interspecies differences in ventilation and respiratory-tract surface areas. Thus, the RDDR can be used to adjust an observed inhalation particulate exposure of an animal to the predicted inhalation exposure for a human. For the subchronic inhalation toxicity study with flumethrin, an RDDR was estimated at 2.7 based on systemic effects (clinical signs of neurotoxicity) at the LOAEL of 1.33 mg /m^3 and a MMAD of 1.06 μm and σ_g of 1.98.

For the registered uses of flumethrin, occupational handler and residential handler scenarios are being assessed. Inhalation exposures of 8 hr/day are assumed for occupational scenarios. HEC and human equivalent dose (HED) calculations are summarized in Table 4.5.1. The standard interspecies extrapolation uncertainty factor can be reduced from 10X to 3X due to the HEC calculation accounting for pharmacokinetic (not pharmacodynamic) interspecies differences. The intraspecies uncertainty factor remains at 10X.

Table 4.5.1: Inhalation HEC and HED Calculation Summary

Population	Scenario	Tox duration adjustment		HEC		HED (mg/kg-day)
		hr/day	day/wk	mg/L	mg/m3	
Occupational	Handler	8	5	0.0002	0.243	0.023
Residential	Handler	NA	NA	0.0003	0.324	0.008
	Outdoor post-application	NA	NA	0.0003	0.324	0.009
	Bystander	24	7	0.0001	0.058	NA

4.5.2 Recommendation for Combining Routes of Exposure for Risk Assessment

HED combines risk values resulting from separate exposure pathways when it is likely they can occur simultaneously based on the use pattern, the behavior associated with the exposed population, and the hazard associated with the points of departure. For flumethrin, the oral, dermal, and inhalation points of departure are based on neurotoxic effects and thus may be combined.

4.5.3 Cancer Classification and Risk Assessment Recommendations

In neither a rat chronic toxicity/carcinogenicity study nor a carcinogenicity mouse study, both conducted with adequate doses, were there treatment related increases in tumor incidences when compared to controls. In accordance with the Agency's 2005 Cancer Guidelines, there was no evidence of carcinogenicity in either species and this chemical is classified as "Not likely to be carcinogenic to humans."

4.5.4 Points of Departure and Toxicity Endpoints Used in Human Risk Assessment

Table 4.5.4: Summary of Toxicological Doses and Endpoints for Flumethrin				
Exposure Scenario	**Dose Used in Risk Assessment, UF**	**Uncertainty/ Safety Factors**	**RfD, PAD, Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Incidental Oral Short-Term (1-30 days)	NOAEL= 0.5 mg/kg/day	UF_A = 10x UF_H = 10x, UF_{DB} = 3x	Residential LOC for individuals < 6 years old = 300	Acute Neurotoxicity Study MIRD 48240215 LOAEL= 1 mg/kg/day in males based on ↓motor/locomotor activity, ↑staining of mouth, perianal, nose, ↑lacrimation, salivation at ↑doses
Dermal Short-term (1-30 days) (< 6 years old)	NOAEL = 10 mg/kg/day	UF_A = 10x UF_H = 10x UF_{DB} = 3x	Residential LOC for MOE = 300	90-day Dermal Study MIRD 48240216 LOAEL=30 mg/kg/day Based on loss of hair; ↓BW and ↓BWG (M), ↓erythrocytes, high stepping gait, ↓ABS spleen wt
Dermal Short-term (1-30 days) (≥ 6 years old)	NOAEL = 10 mg/kg/day	UF_A = 10x UF_H = 10x UF_{DB} = 1x	Residential LOC for MOE = 100 Occupational LOC for MOE = 100	90-day Dermal Study MIRD 48240216 LOAEL=30 mg/kg/day Based on loss of hair; ↓BW and ↓BWG (M), ↓erythrocytes, high stepping gait, ↓ABS spleen wt
Inhalation Short-term (1-30 days) (< 6 years old)	NOAEL = 0.1 mg/m^3	UF_A = 3x UF_H = 10x UF_{DB} = 3x	Residential LOC for MOE = 100	Subchronic inhalation study MIRD 48240219 LOAEL = 1.33 mg /m^3 based on clinical signs of neurotoxicity (bradypnea, labored breathing, red discharge or encrustations from the perinasal area, decreased motility, atony and salivation).
Inhalation (1-30 days) (≥ 6 years old)	NOAEL = 0.1 mg/m^3	UF_A = 3x UF_H = 10x UF_{DB} = 1x	Residential LOC for MOE = 30 Occupational LOC for MOE = 30	Subchronic inhalation study MIRD 48240219 LOAEL = 1.33 mg /m^3 based on clinical signs of neurotoxicity (bradypnea, labored breathing, red discharge or encrustations from the perinasal area, decreased motility, atony and salivation).
Cancer (oral, dermal, inhalation)	**Classification:** "Not likely" to be carcinogenic in humans			

NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). UF_{DB} = database uncertainty, to account for the quantitative susceptibility to children <6 years of age. MOE = margin of exposure. LOC = level of concern. N/A = not applicable.

5.0 Dietary Exposure and Risk Assessment

5.1 Food Residue Profile

There are no currently registered food uses for flumethrin; therefore, residue chemistry data are not required for flumethrin at this time.

5.2 Water Residue Profile

Drinking water exposure is not anticipated based on the registered pet collar uses of flumethrin.

5.3 Dietary Risk Assessment

A dietary (food + drinking water) exposure and risk assessment is not required since there are no currently registered food uses of flumethrin and drinking water exposure is not expected from the registered pet collar uses.

6.0 Residential Exposure and Risk Estimates

SOURCE: Exposure Memo D445425, M. Hawkins, 3/27/2018

Residential handler exposures to the registered flumethrin pet collars may occur while the collars are placed on a cat or dog. Additionally, residential post-application exposures to flumethrin can also occur after collars are placed on a cat or dog via dermal and incidental oral exposure routes. In assessing these exposures, the *Health Effects Division's 2012 Standard Operating Procedures for Residential Pesticide Exposure Assessment: Treated Pets* was used. Due to the uncertainty relating to the physical form of pet collar products (i.e., liquid vs dust), HED has also used chemical- and formulation-specific exposure data submitted by Bayer HealthCare, LLC (Bayer) (MRIDs 48240140, 44433303, 44439901, 45519601, and 501408804) for the assessment of residential handler and post-application exposures and risks.

6.1 Residential Handler Exposure/Risk Estimates

Residential handler exposures to the registered flumethrin pet collars may occur via the dermal and/or inhalation route while the collars are placed on a cat or dog. Residential handler exposure is expected to be short-term in duration (i.e., the flumethrin collar has an 8-month retreatment interval). Intermediate-term exposures are not likely because of the intermittent nature of applications by homeowners. However, the available toxicological data supports the conclusion that neurotoxicity from flumethrin and pyrethroids in general is associated with acute, peak exposures (i.e., every day is a new day). As such, only single day exposure and risks were assessed.

Due to the uncertainty associated with the physical form of pet collar products, a unique approach has been applied in order to account for the potential for exposures from the flumethrin pet collar as both a liquid and solid. The Agency requested that the flumethrin registrants provide information about the physical form of the flumethrin pet collar. Data were submitted by Bayer and were used in conjunction with the 2012 Residential SOPs to account for the relative fraction of liquid and solid active ingredient available for exposure, and to estimate the risks from residential handler and post-application exposures to the flumethrin pet collar.

In order to assess residential handler exposures, the same methodologies described in the 2012 Residential SOPs for assessment of residential handler exposure from pet collar usage were used. However, whereas the 2012 Residential SOPs recommend that pet collars be assessed as a liquid formulation, the approach, used in this risk assessment, assesses the flumethrin pet collar exposures assuming the presence of flumethrin as both a liquid and solid form. For residential handlers, this means use of both liquid and dust applicator unit exposure data as recommended by the 2012 Residential SOPs for these formulation types with an adjustment to account for a 0.9971/0.0029 liquid to dust ratio for flumethrin pet collars. A summary of the submitted data and the approaches used for assessing residential exposures and risks in this assessment are presented in Appendix C.

No chemical-specific unit exposure data were provided in support of this submission and there are currently no surrogate exposure data available for applying pet collars. As a result, HED used exposure data described in the 2012 Treated Pet SOP for spot-on applications (MRID 44433303) and for dust applications (MRIDs 44439901 and 45519601) as health protective surrogates to estimate handler exposures to liquid and dust formulations for applying collars. These unit exposures were based on residential handlers wearing short pants, short-sleeved shirt, and no gloves. In addition to this data, the methodologies and inputs and other standard assumptions (e.g., number of pets treated) were taken from the 2012 Treated Pet SOP, as described in Appendix C.

A total aggregated risk index (ARI) was used since the LOCs for dermal exposure (100) and inhalation exposure (30) are different. The target ARI is 1; therefore, ARIs of less than 1 are risk estimates of concern. The ARI was calculated as follows.

Aggregate Risk Index (ARI) = 1÷ [(Dermal LOC ÷ Dermal MOE) + (Inhalation LOC ÷ Inhalation MOE)]

The residential handler exposure and risk estimates resulting from the assumption of a 0.9971/0.0029 liquid to dust ratio are summarized in Table 6.1.2. When assuming this ratio, residential handler exposures are not of concern for the small or large sized collars (i.e., ARIs ≥ 1).

Table 6.1.2. Residential Handler Non-cancer Exposure and Risk Estimates for Existing Residential Pet Collar Uses of Flumethrin.

Animal Type	Pet Size	Maximum Application Rate (lb ai/collar)[1]	Pets Handled Daily[2]	Combined Dermal MOE[3]	Combined Inhalation MOE[4]	Total ARI[5]
Collar (0.9971 Liquid/0.0029 Dust Ratio)						
Cat	Small	0.00124	2	2,400	4,900	21
	Large	0.00446	2	680	1,400	5.9
Dog	Small (<18 lbs)	0.00124	2	2,400	4,900	21
	Medium (>18 lbs)	0.00446	2	680	1,400	5.9
	Large (18 lbs and up)	0.00446	2	680	1,400	5.9

[1] Small collar application rate: 12.5 gram collar x 4.5% flumethrin x 0.0022 lb/g = 0.00124 lb ai flumethrin per collar. Large collar application rate: 45 gram collar x 4.5% flumethrin x 0.0022 lb/g = 0.00446 lb ai flumethrin per collar.
[2] Based on 2012 Residential SOPs.
[3] Dermal MOE = Dermal NOAEL (10 mg/kg/day) / Dermal Dose (mg/kg/day). Dermal Dose (mg/kg/day) = Exposure * Absorption Factor/Body

Weight) (For Exposure Algorithms see Appendix B).
[4] Inhalation MOE = Inhalation NOAEL (0.008 mg/kg/day) / Inhalation Dose (mg/kg/day). Inhalation Dose =Exposure/Body Weight (For Exposure Algorithms see Appendix B).
[5] ARI = Aggregate Risk Index. 1÷ [(Dermal LOC ÷ Combined Dermal MOE) + (Inhalation LOC ÷ Combined Inhalation MOE)]. Doses and route-specific MOEs are provided in the attached Flumethrin Pet Collar Residential Handler and Post-App_BayerData_Final (3-27-18) Excel Spreadsheet.

6.2 Residential Post-application Exposure/Risk Estimates

Residential post-application exposures to flumethrin can occur from contact with a cat or dog wearing the flumethrin pet collar. Residential post-application inhalation exposure is expected to be negligible from flumethrin pet collars and thus a quantitative assessment was not performed. Dermal post-application risks were assessed for adults and children 1 < 2 years old, and incidental oral (hand-to-mouth) post-application risks were assessed for children 1 < 2 years old.

A pet transferable residue study (i.e., a petting study) was not submitted for flumethrin. However, Bayer submitted a chemical-specific release rate study (MRID 48240140) that measured the amount of flumethrin that was released from small and large collars over the life of the collar (i.e., 8 months or 240 days). Previously, this release rate study was used to estimate transferable residues of flumethrin in order to conduct the assessment of the proposed flumethrin pet collar product.[3] For the current post-application assessment, these transferable residue estimates were used in conjunction with the assumed 0.9971/0.0029 liquid to dust ratio based on the newly submitted chemical- and formulation-specific data. A summary of the submitted data and the approaches used for assessing residential exposures and risks are presented in Appendices B and C.

Release Rate Exposure Data (MRID 48240140): During the proposed new registration of flumethrin collars in 2012 (D392125, C. Smith, 3/6/2012), Bayer submitted release rate data for flumethrin-containing collars. The same methodology that was used in 2012 has been carried over into this registration review assessment. The previous release rate measurements were taken at 30, 60, 90, and 240 days after applying a collar to both cats (small collars) and dogs (large collars). These data do not provide the surface residues of flumethrin on a cat or dog, nor does it provide the amount of flumethrin that could be transferred to a person who contacts a treated cat or dog. Since acute exposures are most toxicologically relevant for flumethrin, HED is most interested in flumethrin residues for the first few days after the collar is applied. The release rate study did not collect any data from these days so for this assessment HED has focused only on the data that was collected at 30 days. Table 6.2 presents a summary of the release rates for flumethrin for both the small and large sized collar.

Since HED is most interested in flumethrin residues for the first few days after collar application, and since pesticide release rates for pet collars are typically higher in the initial days up to a week after application, HED felt that the mg/day value estimated by dividing the 30-day residue value by 30 would underestimate the day 0 residue. Therefore, as a conservative estimate of day 0 residues, it was assumed that the day 0 flumethrin residues would be the total of the first 7 days of release. The day 0 flumethrin residues for small collars is 0.94 mg/day * 7 days that equals

[3] C. Smith. Flumethrin: Human Health Risk Assessment for the Section 3 Registration Action for Cat and Dog Collars. D392125. 3/6/2012.

6.58 mg/day and for large collars is 2.39 mg/day * 7 days that equals 16.73 mg/day. The Bayer study numbers (Table 6.2. below) are used for the release rates were selected since these studies were the only studies that had 1-month measures. The differences measured between the small and large collars can be explained. A summary of the submitted data and the approaches used for assessing residential exposures and risks are presented in Appendices B and C.

Table 6.2. Summary of Flumethrin Released from Small and Large Pet Collars (MRID 48240140)

Bayer Study Number[1]	Collar Size	Study Period (days)	Amount of Flumethrin Released Over Study Period (mg) [2]	Amount of Flumethrin Released per Day (mg/day) [2, 3]	Average Flumethrin Released per Day (mg/day)
146.164	Small	30	42.43	1.41	0.94
146.747			13.7	0.46	
146.165	Large		87.49	2.92	2.39
146.737			55.9	1.86	

1. These study numbers are referenced in MRID 48240140.
2. As summarized in MRID 48240140.
2. Amount of flumethrin released per day (mg/day) = Amount of flumethrin released over study period (mg) / Study Period (days).
3. Assumes the release rate of flumethrin from the collar is consistent across the first 30 days.

Combining Exposure and Risk Estimates

Since dermal, inhalation, and incidental oral exposure routes share common toxicological effects based on neurotoxicity, risk estimates have been combined for those routes, where applicable.

Summary of Residential Post-application Non-Cancer Exposure and Risk Estimates

The residential post-application dermal exposure and risk estimates are summarized in Table 6.2.1. The residential post-application dermal exposure and risk estimates for adults are greater than the LOC (i.e., MOEs ≥ 100) for the small or large sized collars when assuming the 0.9971/0.0029 ratio. The residential post-application combined dermal and incidental oral exposure and risk estimates for children (1 < 2 years old) are greater than the LOC (i.e., MOEs ≥ 300) for the small or large sized collars when assuming a liquid/dust ratio of 0.9971/0.0029 ratio. The risk assessment approaches and studies used for assessment of flumethrin exposures to the Seresto collar are presented in Appendices B and C.

Table 6.2.1. Residential Post-Application Non-cancer Exposure and Risk Estimates for Existing Residential Pet Collar Uses of Flumethrin.

Animal Type	Pet Size	Maximum Application Rate (lb ai/collar)[1]	Pets Handled Daily[2]	Combined Dermal (0.9971 Liquid/0.0029 Dust Ratio) MOE[3] (LOC is an MOE = 100)	Combined Dermal and Incidental Oral (0.9971 Liquid/0.0029 Dust Ratio) MOE[4] (LOC is an MOE = 300)
Collar (0.9971 Liquid/0.0029 Dust Ratio) – Adult					
Cat	Small	0.00124	2	2,100	NA
	Large	0.00446	2	2,200	NA
Dog	Small (<18 lbs)	0.00124	2	4,200	NA

Table 6.2.1. Residential Post-Application Non-cancer Exposure and Risk Estimates for Existing Residential Pet Collar Uses of Flumethrin.					
Animal Type	**Pet Size**	**Maximum Application Rate (lb ai/collar)[1]**	**Pets Handled Daily[2]**	**Combined Dermal (0.9971 Liquid/0.0029 Dust Ratio) MOE[3] (LOC is an MOE = 100)**	**Combined Dermal and Incidental Oral (0.9971 Liquid/0.0029 Dust Ratio) MOE[4] (LOC is an MOE = 300)**
	Medium (>18 lbs)	0.00446	2	3,900	NA
	Large (18 lbs and up)	0.00446	2	6,100	NA
Collar (0.9971 Liquid/0.0029 Dust Ratio) – Children 1 < 2 years old					
Cat	Small	0.00124	2	6,100	1,800
	Large	0.00446	2	6,300	1,900
Dog	Small (<18 lbs)	0.00124	2	12,000	3,600
	Medium (>18 lbs)	0.00446	2	11,000	3,300
	Large (18 lbs and up)	0.00446	2	17,000	5,200

[1] Small collar application rate: 12.5 gram collar x 4.5% flumethrin x 0.0022 lb/g = 0.00124 lb ai flumethrin per collar. Large collar application rate: 45 gram collar x 4.5% flumethrin x 0.0022 lb/g = 0.00446 lb ai flumethrin per collar. (See Table 4.1).
[2] Based on 2012 Residential SOPs.
[3] Dermal MOE = Dermal NOAEL (10 mg/kg/day) / Dermal Dose (mg/kg/day). Dermal Dose (mg/kg/day) = Exposure * Absorption Factor/Body Weight) (For Exposure Algorithms see Appendix B).
[4] Total MOE = POD (mg/kg/day) / (Combined Dermal Dose + Combined Incidental Oral Dose). Doses and route-specific MOEs are provided in the attached Flumethrin Pet Collar Residential Handler and Post-App_BayerData_Final (3-27-18) Excel Spreadsheet.

There are currently no registered food uses for flumethrin and drinking water exposure is not expected from the registered pet collar uses of flumethrin; therefore, a quantitative aggregate risk assessment is not required at this time; therefore, HED has not made recommendations for residential exposure estimates to include in an aggregate assessment.

7.0 Combined Exposure/Risk Characterization

Currently, there are no registered food uses for flumethrin and drinking water exposure is not anticipated from the registered pet collar uses; therefore, a quantitative aggregate risk assessment is not required at this time. The combined risk estimates for residential exposures are not of concern.

8.0 Non-Occupational Spray Drift Exposure and Risk Estimates

A quantitative spray drift assessment was not conducted for the flumethrin pet collar since this use will not result in the potential for spray drift exposures.

9.0 Non-Occupational Bystander Post-Application Inhalation Exposure and Risk Estimates

A quantitative residential post-application inhalation exposure assessment was not performed as inhalation exposure is expected to be negligible from these types of applications. However, an inhalation exposure assessment was performed for handlers (i.e., groomers, treaters, etc.) and this exposure scenario should be considered protective of any potential low-level post-application inhalation exposure that could result from these types of applications.

10.0 Cumulative Exposure/Risk Characterization

The Agency is required to consider the cumulative risks of chemicals sharing a common mechanism of toxicity. The Agency has determined that the pyrethroids and pyrethrins share a common mechanism of toxicity ([HYPERLINK "http://www.regulations.gov"]; EPA-HQ-OPP-2008-0489-0006). As explained in that document, the members of this group share the ability to interact with voltage-gated sodium channels ultimately leading to neurotoxicity. In 2011, after establishing a common mechanism grouping for the pyrethroids and pyrethrins, the Agency conducted a cumulative risk assessment (CRA) which is available at [HYPERLINK "http://www.regulations.gov"]; EPA-HQ-OPP-2011-0746. In that document, the Agency concluded that cumulative exposures to pyrethroids (based on pesticidal uses registered at the time the assessment was conducted) did not present risks of concern. For information regarding EPA's efforts to evaluate the risk of exposure to this class of chemicals, refer to [HYPERLINK "https://www.epa.gov/ingredients-used-pesticide-products/pyrethrins-and-pyrethroids"].

Since the 2011 CRA, for each new pyrethroid and pyrethrin use, the Agency has conducted a screen to evaluate any potential impacts on the CRA prior to those uses being granted. Prior to a final registration review decision for flumethrin, the Agency will determine whether the 2011 CRA needs to be updated based on the availability of any new hazard, use, or exposure information that could potentially change the conclusions of or otherwise impact the 2011 CRA.

11.0 Occupational Exposure and Risk Estimates

SOURCE: Exposure Memo D445425, M. Hawkins, 3/27/2018

Based on the currently registered flumethrin pet collar uses, there is potential for both occupational handler and occupational post-application exposure to occur.

11.1 Occupational Handler Exposure/Risk Estimates

HED uses the term handlers to describe those individuals who are involved in the pesticide application process. HED believes that there are distinct job functions or tasks related to applications and exposures can vary depending on the specifics of each task. Job requirements (amount of chemical used in each application), the kinds of equipment used, the target being treated, and the level of protection used by a handler can cause exposure levels to differ in a manner specific to each application event.

Based on the anticipated use patterns and current labeling, types of equipment and techniques that can potentially be used, occupational handler exposure is expected from the proposed uses. The quantitative exposure/risk assessment developed for occupational handlers is based on the following scenarios:

Applicators:

- RTU Pet Collar – 0.9971 Liquid/0.0029 Dust Ratio Formulation

Occupational Handler Exposure Data and Assumptions

A series of assumptions and exposure factors served as the basis for completing the occupational handler risk assessments. Each assumption and factor is detailed below on an individual basis. Application rate:

Application Rate: The application rates used in this assessment are provided in Table 3.1.

Pet Collar Formulation Assumptions: As was mentioned in the residential sections, due to the uncertainty associated with the ratio of liquid to dust present in the flumethrin products, occupational handler exposures were estimated assuming a 0.9971/0.0029 liquid/dust ratio (i.e., 99.71% liquid and 0.29% dust) exposure based on submitted chemical- and formulation-specific exposure data.

Unit Exposures: It is the policy of HED to use the best available data to assess handler exposure. Sources of generic handler data, used as surrogate data in the absence of chemical-specific data, include PHED 1.1, the AHETF database, the Outdoor Residential Exposure Task Force (ORETF) database, or other registrant-submitted occupational exposure studies. Some of these data are proprietary (e.g., AHETF data), and subject to the data protection provisions of FIFRA. The standard values recommended for use in predicting handler exposure that are used in this assessment, known as "unit exposures", are outlined in the "Occupational Pesticide Handler Unit Exposure Surrogate Reference Table[4]", which, along with additional information on HED policy on use of surrogate data, including descriptions of the various sources, can be found at the Agency website[5].

Area Treated or Amount Handled: The amount handled is based on 8 animals treated daily for pet collars. Refer to Table 11.1.1.

Exposure Duration: Occupational handler exposure is expected to be short- and intermediate-term in duration. The single dose and repeat dosing flumethrin studies show that repeat exposures do not result in lower points of departure (PODs) (i.e., increasing toxicity with increased duration of exposure). Therefore, for the purpose of exposure assessment, only single-day risk assessments need to be conducted.

Mitigation/PPE: Estimates of dermal and inhalation exposure were calculated for various levels of PPE. Results are presented for "baseline," defined as a single layer of clothing consisting of a long-sleeved shirt, long pants, shoes plus socks, no protective gloves, and no respirator.

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[4] Available: [HYPERLINK "http://www.epa.gov/opp00001/science/handler-exposure-table.pdf"]
[5] Available: [HYPERLINK "http://www.epa.gov/pesticides/science/handler-exposure-data.html"]

Occupational Handler Non-Cancer Exposure and Risk Estimate Equations: The algorithms used to estimate non-cancer exposure and dose for occupational handlers can be found in Appendix B.

A total ARI was used since the LOCs for dermal exposure (100) and inhalation exposure (30) are different. The target ARI is 1; therefore, ARIs of less than 1 are risk estimates of concern. The ARI was calculated as follows.

Aggregate Risk Index (ARI) = 1÷ [(Dermal LOC ÷ Dermal MOE) + (Inhalation LOC ÷ Inhalation MOE)]

Summary of Occupational Handler Non-Cancer Exposure and Risk Estimates

A summary of the occupational handler exposure scenarios associated with the registered occupational uses of flumethrin are summarized in Tables 11.1.1.

Table 11.1.1. Occupational Handler Non-cancer Exposure and Risk Estimates for Existing Residential Pet Collar Uses of Flumethrin.

Animal Type	Pet Size	Maximum Application Rate (lb ai/collar)[1]	Pets Handled Daily	Combined Dermal MOE[2]	Combined Inhalation MOE[3]	Total ARI[4]
Collar (0.9971 Liquid/0.0029 Dust Ratio)						
Cat	Small	0.00124	8 animals	650	3,600	6.2
	Large	0.00446		180	1,000	1.7
Dog	Small (<18 lbs)	0.00124		650	3,600	6.2
	Medium (>18 lbs)	0.00446		180	1,000	1.7
	Large (18 lbs and up)	0.00446		180	1,000	1.7

[1] Small collar application rate: 12.5 gram collar x 4.5% flumethrin x 0.0022 lb/g = 0.00124 lb ai flumethrin per collar. Large collar application rate: 45 gram collar x 4.5% flumethrin x 0.0022 lb/g = 0.00446 lb ai flumethrin per collar. Based on registered labels (see Table 3.1).
[2] Dermal MOE = Dermal NOAEL (10 mg/kg/day) / Dermal Dose (mg/kg/day). Dermal Dose (mg/kg/day) = Exposure * Absorption Factor/Body Weight) (For Exposure Algorithms see Appendix B).
[3] Inhalation MOE = Inhalation NOAEL (0.023mg/kg/day) / Inhalation Dose (mg/kg/day). Inhalation Dose =Exposure/Body Weight (For Exposure Algorithms see Appendix A).
[4] ARI = Aggregate Risk Index. 1÷ [(Dermal LOC ÷ Combined Dermal MOE) + (Inhalation LOC ÷ Combined Inhalation MOE). Doses and route-specific MOEs are provided in attached Flumethrin Occupational Handler_PetCollar_Final (3-27-18) Excel Spreadsheet.

11.2 Occupational Post-application Exposure/Risk Estimates

For the registered flumethrin pet collar uses, occupational post-application exposure could potentially occur; however, these types of exposures are not expected to be greater than residential post-application exposures (i.e., minimal and infrequent contact by a professional animal care worker is expected to occur after a collar is applied). As a result, no quantitative occupational post-application exposure and risk assessment has been performed.

12.0 Incident and Epidemiological Data Review

From January 1, 2012 to February 4, 2016, there were was 137 incidents reported to Main Incident Data System (IDS) and 219 incidents reported to Aggregate IDS involving flumethrin (Seresto Collar, EPA Reg. No. 11556-155). Main IDS incidents involving only one pesticide are considered to provide more certain information about the potential effects of

exposure from the pesticide. Thirteen of these incidents were classified as major severity, 124 incidents were classified as moderate severity and 219 incidents were classified as minor severity. Dermal symptoms were reported most often for the major severity incidents, including rash, pruritus and burning sensation. In addition, there was one minor severity incident reported to National Pesticide Information Center (NPIC) involving flumethrin, from January 1, 2011 to December 31, 2015. Flumethrin is not included in the Agricultural Health Study.

The only flumtherin end use product (Seresto Collar, EPA Reg. No. 11556-155) was first registered on March 16, 2012. The Agency will continue to minitor the incident data and if a concern is triggered, additional analysis will be conducted.

13.0 References

Author	Barcode	Date	Title
Hawkins, M.	D445425	3/27/2018	Flumethrin. Occupational and Residential Exposure Assessment for Registration Review.
Recore, S.	D435503	9/7/2016	Flumethrin: Tier I Review of Human Incidents and Epidemiology for Draft Risk Assessment.
Smith, C.	D392125	3/6/2012	Flumethrin: Human Health Risk Assessment for the Section 3 Registration Action for Cat and Dog Collars.

Appendix A: Flumethrin Toxicity Profiles

A.1 Toxicology Data Requirements

Guideline Number and Toxicity Study		Required	Satisfied
870.1100	Acute Oral Toxicity	yes	yes
870.1200	Acute Dermal Toxicity	yes	yes
870.1300	Acute Inhalation Toxicity	yes	yes
870.2400	Primary Eye Irritation	yes	no
870.2500	Primary Dermal Irritation	yes	yes
870.2600	Dermal Sensitization	yes	yes
870.3100	Oral Sub-chronic (Rodent)	CR	yes
870.3150	Oral Sub-chronic (Non-Rodent)	CR	no
870.3200	21-Day Dermal	yes	yes
870.3250	90-Day Dermal	yes	yes
870.3465	90/28-Day Inhalation	CR	yes
870.3700	Developmental Toxicity (Rodent)	yes	yes
870.3700	Developmental Toxicity (Non-rodent)	yes	yes
870.3800	Reproduction	yes	yes
870.4100	Chronic Toxicity (Rodent)	CR	no
870.4100	Chronic Toxicity (Non-rodent)	no	yes
870.4200	Oncogenicity (Rat)	CR	no
870.4200	Oncogenicity (Mouse)	CR	yes
870.4300	Chronic/Oncogenicity	CR	yes
870.5100	Mutagenicity: Gene Mutation - bacterial	yes	yes
870.5300	Mutagenicity: Gene Mutation - mammalian	yes	yes
870.5375	Mutagenicity: Structural Chromosomal Aberrations	yes	yes
870.5395	Mutagenicity: Structural Chromosomal Aberrations	yes	yes
870.5500	Mutagenicity: Other Genotoxic Effects	yes	yes
870.5550	Mutagenicity: Other Genotoxic Effects	yes	no
870.6100	Acute Delayed Neurotoxicity (Hen)	CR	--
870.6100	90-Day Neurotoxicity (Hen)	CR	--
870.6200	Acute Neurotoxicity Screening Battery (Rat)	yes	yes
870.6200	90 Day Neuro. Screening Battery (Rat)	yes	yes
870.6300	Developmental Neurotoxicity	CR	yes
870.7485	General Metabolism	CR	yes
870.7600	Dermal Penetration	CR	no
870.7800	Immunotoxicity	yes	yes

--Not applicable

Appendix A.2. Toxicity Profiles

Table A.2.1: Acute Toxicity Profile – Flumethrin (PC 036007)				
Guideline No.	**Study Type**	**MRID(s)**	**Results**	**Toxicity Category**
870.1100	Acute oral, rat	48240203	LD_{50} Females = 175 mg/kg	II
870.1100	Acute oral, rat	48240204	LD_{50} Males > 100 mg/kg LD_{50} Females = 100 mg/kg	II
870.1200	Acute dermal, rat	48240206	LD_{50} Males = 1998 mg/kg LD_{50} Females = 1436 mg/kg	II
870.1300	Acute inhalation, rat	48240208	LC_{50} Males > 0.585 / <0.812 mg/L LC_{50} Females > 0.277 / <0.585 mg/L	II
870.2400	Acute eye irritation, rabbit	48240211	Waiver requested	IV
870.2500	Acute dermal irritation, rabbit	48240213	Slight irritant; PII=0.25 Bruising observed one animal at 1 hr.	IV
870.2600	Skin sensitization, guinea pig	48240107	Formulation PNR1427 (4.35% flumethrin) is not s sensitizer	No applicable

Table A.2.2: Subchronic, Chronic, and Other Toxicity Profile - Flumethrin			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification/ Doses**	**Results**
870.3100	Subchronic (Oral) Toxicity - Rodent	48240222 (1995) rat Acceptable/guideline 0, 10, 40, 160 ppm (rat) M: 0, 0.7, 2.9, or 11.9 mg/kg/day F: 0, 0.8, 3.4, 13.0 mg/kg/day	NOAEL- 0.7/0.8 mg/kg/day (M/F) LOAEL – 2.9/3.4 mg/kg/day (M/F), ↑extramedullary hematopoiesis; ↓hemosiderin storage; labored breathing; ↑salivation (F); shoulder wounds (M)
		48240224 (1998) mice Acceptable/guideline (mice) 0, 5, 10, **60, 120, 240, 480** ppm **(95.1%, T0059204)** M: 0, 9.9, 20.8, 42.2 mg/kg/day F: 0, 13.2, 26.5, 56.0 mg/kg/day (94.4%, T4060297) M: 0, 0.9, 1.9 mg/kg/day F: 0, 1.4, 2.5 mg/kg/day	NOAEL - 0.9/1.9 (M/F) LOAEL - 1.4/2.5 mg/kg/day, piloerection, dermal lesions, mild hyperkeratosis and acanthosis, emaciation, and mortality at higher doses
870.3250	90 Day Dermal Toxicity - Rat	48240216 (2008) Acceptable/guideline 0, 10, 30, or 80 mg/kg/day	NOAEL - 10 mg/kg/day LOAEL - 30 mg/kg/day, loss of hair; ↓BW and ↓BWG (M), ↓erythrocytes, high stepping gait, ↓ABS spleen wt
870.3200	28 Day Dermal Toxicity - Rat	48240217 (2006) Acceptable/non-guideline 0, 100, 150, 200 mg/kg/day	NOAEL – not established, insufficient number of animals. Clinical signs: bloody muzzle, sunken flanks, reduced motility, high-stepping gait, labored breathing, diarrhea, narrowed eyelids, ↑salivation
	14 Day Dermal Toxicity - Rat	48240218 (2007) Acceptable/non-guideline 0, 10, 30, 100 mg/kg/day	NOAEL – not established, insufficient number of animals. Clinical signs: bloody muzzles, bleedings on nose, hunched backs, reduced motility, high-stepping gait, labored breathing, narrowed eyelids, ↑salivation
870.3700a	Prenatal Developmental Toxicity - Rat	48240225 (1999) Acceptable/guideline 0, 0.75, 2, 5 mg/kg/day	**Maternal** NOAEL – 0.75 mg/kg/day. LOAEL - 2 mg/kg/day, ↓ *H2O, ↓feces, ↓BW/BWG, ↓gravid uterine wt, ↓food consumption*; ↓BW **Developmental** NOAEL – 2 mg/kg/day. LOAEL - 5 mg/kg/day, ↓BW , ↓placenta wt retardation/ossification/microphthalmia
870.3700b	Prenatal Developmental Toxicity – (Rabbit)	48240226 (2009) Acceptable/guideline 0, 0.5, 1.5, 4.5 mg/kg/day	**Maternal** NOAEL – 1.5 mg/kg/day. LOAEL – 4.5 mg/kg/day, Abortions, cold ears, hind limb swelling, soft feces, ↓H2O, ↓urine, enlarged gall bladder, encrusted wounds at throat/forelimbs **Fetal** NOAEL – 1.5 mg/kg/day. LOAEL – 4.5, retarded ossification of metacarpals, phalanges, 1st cervical vertebrae

Table A.2.2: Subchronic, Chronic, and Other Toxicity Profile - Flumethrin			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification/ Doses**	**Results**
870.3800	Reproduction and Fertility Effects	48240227 (2008) 0, 0.5, 1, 3 mg/kg/day Acceptable/guideline Gavage	**Parental** NOAEL not established (M) LOAEL - 0.5 mg/kg/day ↓pituitary in F1 (15%) NOAEL - 0.5 (F) LOAEL - 1.0 mg/kg/day ↓liver weights in F0 & F1 **Reproductive** NOAEL - 3.0 mg/kg/day HDT **Offspring** NOAEL - 1.0 mg/kg/day M/F LOAEL - 3.0 mg/kg/day thinness, no milk spots, ↓BW, ↓rearing indexes with ↑deaths at PND 0-4.
		48240228 (1992) Acceptable/guideline 0, 1, 5, 50 ppm M: 0, 0.05, 0.23, 2.42 mg/kg/day F: 0, 0.06, 0.28, 2.92 mg/kg/day Dietary	**Parental** NOAEL = 0.23 mg/kg LOAEL = 2.42 mg/kg ↓body weight gain in P generation (males), ↓body weight and food consumption in (females) during lactation, ↑postnatal loss in all generations, ↓food consumption in P and F1 males, ↓body weight gain in male and female pups in all generations **Reproductive** NOAEL = 2.42 mg/kg HDT **Offspring** NOAEL – 0.23 mg/kg. LOAEL = 2.42 mg/kg ↓body weight and body weight gains in males and female pups, significantly different testes and ovaries weight, ↓ survival at 21 days
870.3465	Inhalation Toxicity	48240219 (1997) Acceptable/guideline 0.1, 1.4, 20.0 mg/m^3 Analytical 0.12, 1.33 and 22.4 mg/m^3	NOAEL = 0.12 mg/m^3 LOAEL = 1.33 mg /m^3 based on clinical signs of neurotoxicity (bradypnea, labored breathing, red discharge or encrustations from the perinasal area, decreased motility, atony and salivation).
870.4200	Carcinogenicity - Mouse	48240223 (1999) Acceptable/guideline 0, 1,3, 15, 30 ppm M: 0, 0.12, 0.39, 1.97, 4.56 mg/kg/day F: 0, 0.15, 0.52, 2.54, 4.95 mg/kg/day	NOAEL – 0.39/0.52 (M/F) mg/kg/day LOAEL – 1.97/2.54 (M/F) mg/kg/day, ↑skin discoloration, incrustations, sores, missing/deformed ears, epidermal hyperplasia, inflammation, ulceration, M= enlarged/swollen spleens, ↑plasmacytosis mandibular LN, hematopoiesis BM, ↑reduced liver glycogen and hepatocytic atrophy (salivation seen at higher doses, 60ppm↑) There were no increased incidences of treatment related tumors compared to controls
870.4300	Combined Chronic Toxicity/ Carcinogenicity - Rat	42820221 (1999) Acceptable/guideline 0, 0.7, 2, 4 mg/kg/day	NOAEL – 0.7 mg/kg/day LOAEL – 2 mg/kg/day Severe skin lesions, enlarged LN/swollen spleens, plasmacytosis, ↑adrenal cortex vacuolation, no treatment related tumor incidence compared to controls

Table A.2.2: Subchronic, Chronic, and Other Toxicity Profile - Flumethrin			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification/ Doses**	**Results**
870.6200a	Neurotoxicity Screening Battery - Acute - Rat	48240215 (2008) Acceptable/guideline 0, **0.25, 0.50**, 1, 5, 15 mg/kg	NOAEL – 0.5 mg/kg/day in **males** LOAEL – 1.0 (M/F) mg/kg/day, ↓motor/locomotor activity, ↑staining of mouth, perianal, nose, ↑lacrimation, salivation at ↑doses
870.6200b	Neurotoxicity Screening Battery - Subchronic - Rat	48240220 (2008) Acceptable/ guideline 0,1, 2.5, 5 mg/kg/day	NOAEL – 1 mg/kg/day LOAEL – 2.6 mg/kg/day, ↓food consumption, BW/BWG males only, urine/lacrimal/perianal/oral stains, ↓figure8 maze activity (Salivation seen at higher doses)
870.6300	Neurotoxicity Developmental	48240232 (2008) Acceptable/guideline 0, 0.5, 1, 2 mg/kg/day	**Maternal** NOAEL – 1 mg/kg/day LOAEL- 2 mg/kg, BW/day for maternal animals and offspring, based on ↓body weight (-3%) and body weight gain (-9%, $p<0.05$), and ↓food consumption (-15%, $p<0.05$, in dams only). Salivation also seen. **Offspring** NOAEL – 1mg/kg/day LOAEL- 2 mg/kg, ↓ BW in M on PND 11 and 17 (- 8%, $p<0.01$) and in the low and high dose F on PND 11 (-6%, $p<0.05$) and were associated with significant reduced body weight gain that began on PND 4-11. In addition, body weight was non-statistically decreased on PND 21 in M. This difference in body weight for males persisted to study termination (statistically decreased 6-7% compared to control).
870.5100	Bacterial Reverse Mutation Test	48240233 (1993) Acceptable/guideline 0, 8, 40, 200, 1000, and 5000 µg/plate (with and without activation)	There was no evidence of induced reverse mutations with or without activation. [Negative]
		48240234 (1993) Unacceptable/non-guideline 0, 7500, 10,000, 12,500, 15,000 µg/plate (with and without activation)	There was no evidence of induced reverse mutations with or without activation. [Negative]

Table A.2.2: Subchronic, Chronic, and Other Toxicity Profile - Flumethrin			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification/ Doses**	**Results**
		48240235 (2006) Acceptable/guideline 0, 16, 50, 158, 500, 1581 and 5000 ug/per plate (with and without activation)	There was no evidence of induced reverse mutations with or without activation. [Negative]
870.5300	In vitro mammalian cell gene mutation test	48240236 (1995) Acceptable/guideline 0, 6.25, 12.5, 25, 50, 75, and 100 µg/mL (with and without activation)	There was no evidence of induced reverse mutations with or without activation. [Negative]
		48240237 (2007) Acceptable/guideline 0, 25, 50, or 100 µg/mL	There was no evidence of chromosomal aberrations. [Negative]
		48240239 (2007) Acceptable/guideline 0, 6, 12, 24, 48, 96 or 182 µg/mL	There was no evidence of induced reverse mutations with or without activation. [Negative]
870.5375	In vitro mammalian chromosome aberration test	48240238 (1995) Acceptable/guideline 100, 200, 500, 1000, 2500, or 5000 µg/mL (with and without activation)	There was no evidence of induced reverse mutations with or without activation. [Negative]
870.5395	Mammalian erythrocyte micronucleus test	48240240 (2007) Acceptable/guideline 0, 125, 250, 500 mg/kg	This chemical was not found to be clastogenic or aneugenic. [Negative]
		48240241 (1995) Acceptable/guideline 0, 1000mg/kg	There was no evidence of chromosomal aberrations with or without activation. [Negative]
870.5500	Unscheduled DNA Synthesis *in vitro*	48240242 (1994) Acceptable/guideline 0, 5, 10, 50, 100, 200, 300, 500 µg/mL	There was no evidence of genotoxic activity. [Negative]

Table A.2.2: Subchronic, Chronic, and Other Toxicity Profile - Flumethrin			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification/ Doses**	**Results**
870.7485	Metabolism and pharmacokinetics	48240243 (1992) Acceptable/guideline 1, 5 mg/kg	Radioactivity administered with [Cl-phenyl-U-^{14}C] flumethrin was rapidly but incompletely absorbed from the intestinal lumen of rats. Excretion of the compound was slow and mostly in the feces comprising 77-88 % of the dose. The majority of the radioactive feces eliminated had been absorbed and excreted with the bile into the gut lumen. The highest amount of radioactivity in the body was mainly found in the plasma, which at sacrifice showed the highest residue concentration in dose groups tested. All other organs exhibited significantly lower concentrations. The lowest values were determined in the brain, indicating that the blood-brain barrier is almost impermeable for the test compound and its labeled metabolites. The radioactive residues in the body excluding the gastrointestinal tract at sacrifice, seven days after dosing, were still relatively high, varying between 9 % and 20 % of the given dose. The multiple dose experiment clearly showed an accumulation of the radioactivity in the body. The 24 hour dosing interval was too short to completely allow for the elimination of the administered radioactivity. Since the renal excretion played only a negligible role, metabolite identification was conducted exclusively in the feces.
		48240244 (2000) Acceptable/non-guideline 0, 50, 160ppm	Mean plasma concentration of flumethrin and flumethrin granules after 3, 6, 13 weeks of 160ppm were bioavailability were similar
870.7800	Immunotoxicity	48240250 (2009) Acceptable/guideline 0, 10, 40, 160 ppm 0, 0.8, 3, 11.7 mg/kg/day M 0, 1, 3.5, 12.3 mg/kg/day F	Systemic NOAEL- 3/3.5 LOAEL-11.7/12.3 (M/F) ↓BW (significant in week 1 only for F)
Non-guideline	4-week Gavage Pilot, for 2-Gen rat repro	48240229 (2006) Acceptable/non-guideline 5.0, 7.5,10.0 mg/kg/day	Males NOAEL- Not established. LOAEL = 5 mg/kg/day (HDT) ↓reduced mean relative spleen and thymus weights and ↓absolute thymus and spleen weight. Females LOAEL - 10 mg/kg/day slightly ↓ mean body weight and reduced mean absolute and spleen weights Female NOAEL = 7.5 mg/kg/day

Table A.2.2: Subchronic, Chronic, and Other Toxicity Profile - Flumethrin			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification/ Doses**	**Results**
Non-guideline	Rat Plasma – Gavage, 2 –Gen rat repro	48240245 (2007) Acceptable/non-guideline 0, 0.5, 1.0, or 3.0 mg/kg/day	Plasma concentration study, a part of the 2-generation reproduction study no. (MRID 48240227), The animals were grouped into one control and 3 dose groups per sex and generation. All results for control group animals were below the limit of quantification. Results obtained from rats in the various dose groups showed a clear dose-concentration relation. The highest concentrations were found four hours after dosing. The concentration results for male animals were significant higher than for females.
Non-guideline	Rat Plasma – Pilot with MRID 48240230	48240231 (2006) Acceptable/non-guideline 0.08, 0.4 or 2 mg/kg/day	This study was part of an exploratory subchronic oral toxicity study (MRID 48240230) in which plasma was collected from male and female rats and analyzed to determine plasma concentrations of flumethrin. Maximum plasma levels were measured at 2 to 4 hours after administration at each dose level. At the dose concentration between 0.4 and 2.0 mg/kg there was a clear increase of plasma levels with dose that was visible in both sexes. Continuing plasma level increases were not seen in the dosage range of 3.0 to 5.0 mg/kg (after enhanced dose scheme).
Non-guideline	19-week Gavage Pilot, for 2-Gen rat repro	48240230 (2006) Acceptable/non-guideline 0, 0.08, 0.4, 2.0 mg/kg/day After day 70: 3, 4, 5 mg/kg/day	**Parental male** NOAEL- 3 mg/kg/day LOAEL - 4 mg/kg/day ↓slightly body weight. **Parental female** NOAEL - 2 mg/kg/day lack of effects prior to dose elevation LOAEL- 3 mg/kg/day ↓bw during pregnancy. **Offspring** NOAEL –2 mg/kg/day LOAEL = 3 mg/kg/day The body weight changes were insignificant for M/F. ↑absolute adrenal wt in F ($p<0.01$) and ↓thymus weight in males- 3, 4 mg/kg/day.

Appendix A.3. Hazard Identification and Endpoint Selection

A.3.1 Acute Reference Dose (aRfD) - All Populations

Acute dietary endpoints were available to quantify risk to all populations, including infants and children. However, no PODs were chosen since the exposure scenarios did not warrant such values to be assessed.

A.3.2 Chronic Reference Dose (cRfD)

Chronic endpoints have not been chosen for flumethrin since the exposure scenarios did not warrant such values to be assessed.

A.3.3 Incidental Oral Exposure (Short-Term)

The NOAEL of 0.5 mg/kg/day from the acute neurotoxicity study is selected for this endpoint due to the overall consistency of the database and the exposure scenario of this study. The POD identified in the ACN study is found to be protective and captures the dose spread for the 2-generation reproductive study which has a lower identified NOAEL (0.23 mg/kg/day). The Hazard Identification and Endpoint Selection graph A.3 portrays the nearly flat dose-response for does which elicit many of the clinical signs seen in the database, and moreover, within these two studies. There were clear signs of increased salivation, lacrimation, and decreased motor and locomotor activity in both sexes at the LOAEL of 1.0 mg/kg /day. Therefore, the exposure scenario combined with the overlap in doses which produced an adverse effect due to treatment within the acute neurotoxicity study gave more confidence in the data.

A.3.4 Dermal Exposure (Short-Term)

The 90-day dermal study in rats with NOAEL of 10 mg/kg/day was selected for this endpoint. The LOAEL value of 30 mg/kg/day was based on observations of clinical signs (high stepping gait), and decreased body weight and weight gain. Since a dermal toxicity study is selected for dermal risk assessment, a dermal-absorption factor is not required.

A.3.5 Inhalation Exposure (Short-Term)

The subchronic inhalation study with a NOAEL of 0.1 mg/m^3 was selected for this endpoint. The LOAEL of 1.33 mg/m^3 is based on the results from clinical signs of toxicity battery of reflex tests and lung function measurements, hematology and clinical chemistry.

Appendix B. Residential and Occupational Exposure Algorithms and Standard Inputs

Residential Dermal Handler Exposure Algorithm for Pet Collars

Daily dermal exposure (mg/day) for residential pesticide handlers is estimated by multiplying the formulation-application method-specific unit exposure by an estimate of the amount of active ingredient handled in a day adjusted by the liquid or dust fraction estimated to be present, using the equation below:

$$E = UE * AR * A$$

where:

E = exposure (mg/day);
UE = unit exposure (mg/lb ai);
AR = application rate (e.g., lb ai/ft^2, lb ai/gal); and
A = number of animals treated per day.

The AR is adjusted to represent the liquid fraction by multiplying by the fraction of liquid assumed to be present (0.9971) and for the dust fraction by multiplying by the fraction of dust assumed to be present (0.0029).

Absorbed dermal dose normalized to body weight is calculated as:

$$D = \frac{E * AF}{BW}$$

where:

D	= dose (mg/kg-day);
E	= exposure (mg/day);
AF	= absorption factor (dermal and/or inhalation); and
BW	= body weight (kg).

Residential Post-Application Dermal Exposure Algorithm

The following method is used to calculate dermal exposures that are attributable to an adult or child contacting a treated companion pet:

$$E = TC * (TR_{Dust} \text{ or } TR_{Liquid}) * ET$$

where:

E	= exposure (mg/day);
TC	= transfer coefficient (cm^2/hr);

$TR_{dust\ or\ liquid}$ = dust or liquid transferable residue (mg/cm^2); and
ET = exposure time (hours/day).

$$TR_{dust\ or\ liquid} = \frac{(CSR_{Dust}\ or\ CSR_{Liquid}) * F_{AR}}{SA}$$

Where:

$TR_{dust\ or\ liquid}$ = dust or liquid transferable residue (mg/cm^2);
CSR_{Dust} = collar surface dust residues (mg);
CSR_{Liquid} = collar surface liquid residues (mg);
F_{AR} = fraction of the CSR available as transferable residue; and
SA = surface area of the pet (cm^2).

$$CSR_{Dust\ or\ Liquid} = RR * F_{Dust\ or\ Liquid}$$

Where:

$CSR_{Dust\ or\ Liquid}$ = collar surface dust or liquid residues (mg);
RR = release rate of flumethrin or imidacloprid (mg); and
F_{Dust} = fraction of dust (0.0029) or liquid (0.9971).

Absorbed dermal dose, normalized to body weight, is calculated as:

$$D = \frac{E * AF}{BW}$$

where:

D = dose (mg/kg-day);
E = exposure (mg/day);
AF = absorption factor (dermal); and
BW = body weight (kg).

The doses resulting from the liquid and dust fractions are calculated separately, and then added together to get a total dose resulting from exposure to the pet collar.

Table B.1. Treated Pets – Inputs for Residential Post-Application Dermal Exposure From the Seresto Collar

Algorithm Notation	Exposure Factor Units	Point Estimates
RR	Release Rate of Flumethrin Small Collar (12.5 g) (mg)	6.6 (0.94 * 7 days)
	Release Rate of Flumethrin Large Collar (45 g) (mg)	16.7 (2.39 * 7 days)
	Release Rate of Imidacloprid Small Collar (12.5 g) (mg)	58.5 (8.35 * 7 days)
	Release Rate of Imidacloprid Large Collar (45 g)	159

Table B.1. Treated Pets – Inputs for Residential Post-Application Dermal Exposure From the Seresto Collar			
Algorithm Notation	**Exposure Factor Units**		**Point Estimates**
	(mg)		(22.7 * 7 days)
SA	Surface Area of Animal (cm^2)	Small Cat, Dog	Cat – 1,500 Dog – 3,000
		Medium Cat, Dog	Cat – 2,500 Dog – 7,000
		Large Cat, Dog	Cat – 4,000 Dog – 11,000
F_{Dust}	Fraction of dust		0.0029
F_{Liquid}	Fraction of liquid		0.9971
F_{AR}	Fraction of CSR Available for Transfer (recommended point estimate)		0.02
TC	Transfer Coefficient – Liquids (cm^2/hr)	Adult	5,200
		Children 1 < 2 years old	1,400
	Transfer Coefficient – Solids (cm^2/hr)	Adult	140,000
		Children 1 < 2 years old	38,000
ET	Exposure Time (hours per day)	Adult	0.77
		Children 1 < 2 years old	1.0
BW	Body weight (kg)	Adult	80
		Children 1 < 2 years old	11

Residential Post-application Hand-to-Mouth Exposure Algorithm

Exposure from hand-to-mouth activity is calculated as follows (based on algorithm utilized in SHEDS-Multimedia):

$$E = [HR * (F_M * SA_H) * (ET * N\_Replen) * (1- (1- SE)^{(Freq\_HtM/N\text{-}Replen)})]$$

where:

E = exposure (mg/day);
HR = hand residue loading (mg/cm^2);
SA_H = surface area of one child hand (cm^2);
F_M = fraction hand surface area mouthed /event (fraction/event);
ET = exposure time (hr/day);
N_Replen = number of replenishment intervals per hour (intervals/hour);
SE = saliva extraction factor (i.e., mouthing removal efficiency); and

Freq_HtM = number of hand-to-mouth contacts events per hour (events/hour).

and

$$HR = \frac{E * Fai_{hands}}{2 * SA_H}$$

where:

HR = hand residue loading (mg/cm^2);
E = dermal exposure (mg);
Fai_{hands} = fraction of a.i. on hands compared to total residue from dermal transfer coefficient study (unitless); and
SA_H = surface area of one child hand (cm^2).

Oral dose, normalized to body weight, is calculated as:

$$D = \frac{E}{BW}$$

where:

D = dose (mg/kg-day);
E = exposure (mg/day); and
BW = body weight (kg).

Table B.2. Treated Pets – Inputs for Residential Post-application Hand-to-Mouth Exposure

Algorithm Notation	Exposure Factor (units)		Point Estimate(s)
Fai_{hands}	Fraction of a.i. on hands from transfer coefficient studies (unitless)		Solid = 0.37 Liquid = 0.040
F_M	Fraction hand surface area mouthed /event (fraction/event)		0.13
N_Replen	Replenishment intervals per hour (intervals/hr)		4
ET	Exposure time (hours/day)	Children 1 < 2 years old	1.0
SE	Saliva extraction factor		0.48
Freq_HtM	Hand-to-mouth events per hour (events/hr)	Children 1 < 2 years old	20
SA_H	Typical surface area of one child hand (cm^2)	Children 1 < 2 years old	150
BW	Body Weight (kg)	Children 1 < 2 years old	11

Occupational Non-cancer Handler Algorithms

Potential daily exposures for occupational handlers are calculated using the following formulas:

$$E = UE * AR * A * 0.001\ mg/ug$$

where:

E	=	exposure (mg ai/day),
UE	=	unit exposure (µg ai/lb ai),
AR	=	maximum application rate according to proposed label (lb ai A or lb ai/gal), and
A	=	area treated or amount handled (e.g., A/day, gal/day).

The AR is adjusted to represent the liquid fraction by multiplying by the fraction of liquid assumed to be present (0.9971) and for the dust fraction by multiplying by the fraction of dust assumed to be present (0.0029).

The daily doses are calculated using the following formula:

$$ADD = \frac{E * AF}{BW}$$

where:

ADD	=	average daily dose absorbed in a given scenario (mg ai/kg/day),
E	=	exposure (mg ai/day),
AF	=	absorption factor (dermal and/or inhalation), and
BW	=	body weight (kg).

Margin of Exposure: Non-cancer risk estimates for each application handler scenario are calculated using a Margin of Exposure (MOE), which is a ratio of the toxicological endpoint to the daily dose of concern. The daily dermal and inhalation dose received by occupational handlers are compared to the appropriate POD (i.e., NOAEL) to assess the risk to occupational handlers for each exposure route. All MOE values are calculated using the following formula:

$$MOE = \frac{POD}{ADD}$$

where:

MOE	=	margin of exposure: value used by HED to represent risk estimates (unitless),
POD	=	point of departure (mg/kg/day), and
ADD	=	average daily dose absorbed in a given scenario (mg ai/kg/day).

Appendix C. Pet Collar Formulation Type/Risk Assessment Approach

Due to the uncertainty associated with the physical form of pet collar products, the Agency has begun efforts to reevaluate pet collar formulations to carefully consider whether pet collar product active ingredients are released as a liquid or solid form, and, if determined to be both, the relative fraction of each. In following with this evaluation, the Agency intends to request and review additional information relating to all registered pet collar products as they undergo Registration Review, as well as any proposed new pet collar uses. This evaluation will continue until the Agency is satisfied that, based on the design and operation of pet collar products, a final formulation type decision can be made along with recommendations for human health risk assessment of exposures to pet collar-treated pets.

MRID 50140804: Flumethrin Release from Seresto Collars by Torsional Stressing. M. Hammer. 12-20-2016.

Bayer HealthCare, LLC conducted a study to determine the amount of solid (dust) material present on the Seresto collar surface under extreme mechanical stress. Per the study report, when a Seresto collar is subjected to extreme mechanical stress, which is unlikely to be observed in typical use, it releases a small amount of white-grey powder to the collar surface. A test plate with the same composition and texture as a Seresto collar was subjected to extreme stress by torsion or stretching. A test plate was used due to the complex design of the Seresto collar (e.g., areas of various thickness inherent to the collar design) which would potentially have complicated 1) application of uniform torsion (i.e., the same amount of physical force would have resulted in different actual torsion for thin versus thick areas) and 2) thoroughness of wiping of the collar around grooves and ridges. A test plate with homogenous, well-defined configuration was used in order to produce more accurate results (e.g., mg dust per surface). The test plate was representative of the Seresto collar since the composition of the test plate was exactly the same as that of the Seresto collar. Although the plate only represented a portion of the collar, it allows for estimation of the fraction of dust generated under extreme mechanical stress. The test plate was twisted 10 times for 180°. The test plate used was 58 x 20 x 2.9 mm with a mass of 4.1 grams. Under extreme mechanical torsion, 10 to 12 mg of a small amount of a white-grey powder, or dust, was wiped off with tissue paper. Using the more conservative measure of the range, 12 mg, results in an estimate of 0.29% of the collar by weight dust generation (i.e., 12 mg dust released on the surface of the collar/ 4,100 mg test plate = 0.0029).

MRID 50140803: Imidacloprid/Flumethrin 10%/4.5 % Collar (all sizes) – Investigation of Composition of Surface Abrasion after Mechanical Stress. W. Jiritschka.11-15-2011.

Bayer conducted a study to determine the quantitative composition of the abrasion, or the dust generated by torsion, from a Seresto collar after mechanical stress. A large collar was removed from the packaging and squeezed and distorted several times. The study report describes that this level of mechanical stress is unusual, but was necessary in order to force bound material to the outside of the collar matrix sufficient to generate dust for examination. Solid white particles (dust), very loosely bound to the collar surface, were removed for analysis. The concentrations of imidacloprid and flumethrin in the yielded powder were determined in duplicate with a specific, validated high-performance liquid chromatography (HPLC) method (AM-VET 115).

The study concluded that the powder consisted of approximately 45% imidacloprid, 47% stearic acid, and 0.05 – 0.2 % flumethrin. An observed lack of mass balance of 8% of the powder was reported to likely be caused by plasticizers.

The study report added that the mechanical stressing of the collars results in far greater release of the collar active ingredients than was observed in the release rate study submitted which was conducted under conditions of normal wear by a cat or dog. Further, the report describes that the amount of imidacloprid observed is a result of a "microlayer" embedded within the collar being forced to the surface through mechanical stress. The more lipophilic flumethrin is released in very low amounts in both the mechanical torsion and dust composition studies since it is more lipophilic than imidacloprid and, thus, remains imbedded in the collar matrix.

Risk Assessment Approach

A unique approach has been applied in order to account for the potential for exposure to the flumethrin in a pet collar as both a liquid and solid form. The approach uses the same methodologies described in the 2012 Residential SOPs for assessment of residential handler and post-application exposure assessment for pet collar usage. However, whereas the 2012 SOPs recommend that pet collars be assessed as a liquid formulation only, the present approach, used in this assessment, assessed exposures from the flumethrin pet collar as both a liquid and solid form with use of the chemical-specific data submitted by the product registrant, Bayer HealthCare, LLC, and the exposure-specific data provided in the 2012 SOPs. As described in Section 6.2, Bayer previously submitted a chemical-specific exposure study (MRID 48240140) that measured the amount of flumethrin that was released from the small and large collars over the life of the collar. The release rate study was used in 2012 to estimate transferable residues of flumethrin and imidacloprid for assessment of the proposed Seresto pet collar product. The resulting daily release rate measures are presented in Section 6.2. The release rate study was conducted in a manner that reflects actual wear by cats and dogs and is, therefore, thought to be a realistic representation of flumethrin and imidacloprid residues available on the collar surface over time. However, release rate measurements were taken at 30, 60, 90, and 240 days after application of the collar to cats and dogs. Since HED is most interested in flumethrin and imidacloprid residues for the first few days after collar application, and since pesticide release rates for pet collars are typically higher in the initial days up to a week after application, HED felt that the mg/day value estimated by dividing the 30-day residue value by 30 would underestimate the day 0 residue. Therefore, as a conservative estimate of day 0 residues, it was assumed that the day 0 flumethrin and imidacloprid residues would be the total of the first 7 days of release. Further, the release rate study was not designed with the intent of determining the form of the available residues (liquid vs dust). Therefore, additional data were required to determine the physical form of the available flumethrin and imidacloprid residues.

Based on the review of the studies submitted relating to the physical form of residues released from the Seresto collar, HED has estimated a 99.71% liquid to 0.29% dust ratio for flumethrin. This assumption relies on the mechanical torsion study (MRID 50140804). Under extreme mechanical torsion, 10 to 12 mg of a small amount of a white-grey powder, or dust, was wiped off with tissue paper. Using the more conservative measure of the range, 12 mg, results in an estimate of 0.29% of the collar by weight dust generation (i.e., 12 mg dust released on the

surface of the collar/ 4,100 mg test plate = 0.0029). HED acknowledges that the torsion study, which subjected test plates of the Seresto collar to extreme mechanical stress, is unlikely to be observed in typical use and may potentially overestimate the generation of solids, or dusts, from normal wear by cats or dogs. However, these were the only data submitted that were determined useful for the purpose of evaluating the Seresto collar physical form.

For the quantification of residential and occupational handler exposures to the Seresto collar, both the liquid and dust applicator unit exposure (UE) data, as recommended by the 2012 Residential SOPs for these formulation types, were used with an adjustment to account for a 99.71/0.0029 liquid to dust ratio.

For residential post-application exposures to the Seresto collar, the Treated Pet SOP algorithm was modified to account for the fraction of dust versus liquid present on the collar. An additional input, collar surface residue (CSR), was calculated for both the dust and liquid forms. The CSR_{Dust} input is quantified by multiplication of the total daily release rate for flumethrin or imidacloprid (small and large collar) by the fraction of dust (0.0029) anticipated to be available on the surface of the collar. CSR_{Liquid} input is quantified in similarly, but using the fraction of liquid (0.9971) anticipated to be available (in effect assuming that all surface residues remaining after accounting for the dust fraction are a liquid form). CSR_{Dust} and CSR_{Liquid} were then input into the standard SOP dermal exposure algorithm to estimate the dust and liquid transferable residues. The dust and liquid TRs were then used to estimate separate dermal doses. These doses were combined to result in a total dermal exposure estimate for each active ingredient and small/large collar combination. Since dermal exposures are the basis of children's incidental oral exposures to pets, a separate incidental oral exposure was also estimated for each dust/liquid and active ingredient combination, and then combined to result in a total incidental oral exposure estimate. For both flumethrin and imidacloprid, the dermal and incidental oral endpoints are based on the same effect and, therefore, these total dust + liquid dermal and incidental oral risk estimates are combined. The algorithms and inputs used are presented above in Appendix B.

HED chose not to use the dust composition study (MRID 50140803) data in conjunction with the torsion study to estimate Day 0 residues. The use of these data combined is believed to be inappropriate due to a number of reasons. First, since the torsion study is not representative of normal wear and likely overestimates the dust fraction, the use of the dust composition data in this manner would result in an unrealistic overestimate of available residues. Second, the dust composition study collected dust samples from a large collar and not from the test plate used in the mechanical torsion study. Therefore, it is uncertain whether the dust collected from the torsion study would be expected to have similar percentages of active ingredients as the large collar. Finally, the use of the release rate data is likely conservative (i.e., the assumption of 7 day residue release occurring on Day 0). Therefore, the release rate data paired with the fraction dust formation from the mechanical torsion study are believed to result in a conservative estimate of exposures to the Seresto collar.